HANNA AINIALA

Neuropsychiatric Involvement in Systemic Lupus Erythematosus

ACADEMIC DISSERTATION
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ORIGINAL COMMUNICATIONS

LIST OF ORIGINAL COMMUNICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I **Ainiala H**, Loukkola J, Peltola J, Korpela M, Hietaharju A. The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus. Neurology 2001;57:496-500.

II **Ainiala H**, Hietaharju A, Loukkola J, Peltola J, Korpela M, Metsänoja R, Auvinen A. Validity of the new American College of Rheumatology criteria for neuropsychiatric lupus syndromes: a population-based evaluation. Arthritis Care and Research 2001;45:419-423.

III **Ainiala H**, Hietaharju A, Dastidar P, Loukkola J, Lehtimäki T, Peltola J, Korpela M, Heinonen T, Nikkari S. Increased serum matrix metalloproteinase 9 levels in systemic lupus erythematosus patients with neuropsychiatric manifestations and brain magnetic resonance imaging abnormalities. Arthritis Rheum 2004;50:858-865.

IV **Ainiala H**, Dastidar P, Loukkola J, Lehtimäki T, Korpela M, Peltola J, Hietaharju A. Cerebral MRI abnormalities and their association with neuropsychiatric manifestations in SLE – a population-based study. Scand J Rheumatol 2005;34:376-82.

ABREVIATIONS

ACL	Anticardiolipin antibodies
ACR	American College of Rheumatology
ANA	Antinuclear antibodies
Anti-dsDNA-ab	Anti-double stranded DNA antibodies
APL	Antiphospholipid antibodies
APS	Antiphospholipid syndrome
ARA	American Rheumatism Association
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computer tomography
DNA	Deoxyribonucleic acid
ECLAM	European Consensus Lupus Activity Measurement
ENA	Extractable nuclear antigens
ENMG	Electroneuromyography
GN	Glomerulonephritis
HCQ	Hydroxychloroquine
Ig	Immunoglobulin
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MTI	Magnetic transfer imaging
NP	Neuropsychiatric
NPSLE	Neuropsychiatric systemic lupus erythematosus
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
TIA	Transient ischemic attack

ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting multiple organ systems. Neuropsychiatric (NP) manifestations are a major cause of morbidity and mortality in patients with SLE. The prevalence of NPSLE ranges widely reflecting variable diagnostic criteria and differences in selection of patients for study. The pathogenesis of NPSLE is still unclear. This study was done to describe the prevalence of NP syndromes in a Finnish population of patients with SLE and classify them according to the American College of Rheumatology (ACR) nomenclature and case definitions for NPSLE; to assess the validity of the ACR nomenclature system; to evaluate whether serum matrix metalloproteinase-9 (MMP-9) levels are associated with NP manifestations and to evaluate the volumetric brain magnetic resonance imaging (MRI) findings in SLE patients.

The study group consisted of 46 SLE patients and an equal amount of matched controls. A complete medical history was obtained from all and a clinical neurological examination was performed by the same neurologist. All past and present NP syndromes were listed and classified according to the ACR nomenclature and case definitions. Individual disease activity and an accumulated NP abnormality were assessed by using standardized scores. A cumulative lifetime dose of glucucorticoids was derived from the medical records. Laboratory tests including anticardiolipin antibodies and a quantification of immunoreactive MMP-9 were done for all. A battery of standardized neuropsychological tests and a clinical interview by the psychologist were performed in order to detect a possible cognitive deficit, depression or anxiety disorder. Cerebral MRI was done for all study subjects. Volumetric measures of cerebral atrophy as well as T1- and T2-weighted lesions were obtained.

At least one NP syndrome was identified in 91% of SLE patients in this population-based study. Cognitive dysfunction was the most frequent single manifestation followed by headache and mood disorder. When mild NP syndromes (mild cognitive deficit, headache, mild depression, anxiety and polyneuropathy with normal ENMG findings) were excluded, the prevalence of NPSLE dropped to 46%.

All NPSLE syndromes were more frequent among SLE patients than controls. However, most syndromes were also found among controls, which resulted in low specificity. To improve the criteria we constructed revised criteria based on objective findings only. We entirely excluded mild

NP syndromes and with this modification, the proportion of controls fulfilling at least 1 of the criteria was substantially lower (7% versus 54%).

No significant difference was found in serum MMP-9 levels between the overall group of SLE patients and controls. However, patients with at least one NP manifestation had significantly higher MMP-9 concentrations than SLE patients without NP syndromes. Among SLE patients, those with cognitive deficits had significantly higher MMP-9 concentrations than did those with normal cognitive function. Furthermore, serum MMP-9 levels correlated positively with the volumes of T1- and T2-weighted lesions in the brain MRI.

Compared with controls, SLE patients had increased volumes of both T1- and T2-weighted lesions and increased cerebral atrophy in brain MRI. Cerebral atrophy was associated with cognitive dysfunction, epileptic seizures and cerebrovascular disease; T1-weighted lesions with epileptic seizures and T2-weighted lesions with cognitive dysfunction. A positive correlation was found between a cumulative dose of glucocorticoids and cerebral atrophy in SLE patients.

As a summary, the prevalence of NPSLE in a population-based sample of SLE patients was 91% by using ACR nomenclature and case definitions, and 46% when our revised criteria based on neurologic injury and exclucion of mild NP syndromes, was used. ACR criteria for NPSLE were not able to differentiate SLE patients from controls. In cerebral MRI, brain atrophy, cerebrovascular and demyelinating lesions were more common in patients with SLE than in general population, and associated with certain NP manifestations. Elevated levels of serum MMP-9 in patients with SLE may indicate NP involvement, especially cognitive dysfunction.

TIIVISTELMÄ

Systeeminen lupus erythematosus (SLE) on useisiin elinjärjestelmiin vaikuttava autoimmuunisairaus. Neuropsykiatriset (NP) ilmenemismuodot ovat suuri sairastavuuden ja kuolleisuuden syy SLE:ssä. NPSLE:n prevalenssi vaihtelee suuresti riippuen tutkimuksessa käytetyistä diagnostisista kriteereistä ja potilasvalinnasta. NPLSE:n patogeneesi on tuntematon.

Tämän tutkimuksen tarkoituksena oli selvittää NP ilmenemismuotojen prevalenssia suomalaisilla SLE-potilailla väestöpohjaisessa otannassa ja luokitella syndroomat American College of Rheumatologyn (ACR) laatiman NPSLE:n luokittelujärjestelmän pohjalta; arvioida ACR:n luokittelujärjestelmän validiteettia; selvittää, onko seerumin matriksin metalloproteinaasi-9:llä (MMP-9) yhteys NP ilmenemismuotoihin ja tutkia aivojen magneettikuvalöydöksiä (MK) SLE-potilailla.

Tutkimusryhmä koostui 46 SLE-potilaasta ja yhtä monesta vakioidusta verrokkihenkilöstä. Heidän sairaushistoriansa selvitettiin ja sama neurologi teki kaikille kliinisen neurologisen tutkimuksen. Kaikki aiemmat ja nykyiset NP-syndroomat luetteloitiin ja luokiteltiin ACR:n luokittelujärjestelmän perusteella. Sairauden aktiviteetti ja kumulatiivinen NP vaurioaste määritettiin standardoiduilla asteikoilla. Elinikäinen glukokortikoidien kokonaisannos laskettiin sairauskertomustietojen perusteella. Kaikilta tutkimukseen osallistujilta otettiin laboratoriokokeita sisältäen immunoreaktiivisen MMP-9:n määrityksen. Mahdollisen kognitiivisen eli tiedonkäsittelyn häiriön, depression ja ahdistuneisuuden toteamiseksi tehtiin neuropsykologinen tutkimus ja psykologin suorittama kliininen haastattelu. Kaikille tutkittaville tehtiin aivojen MK, jonka perusteella määritettiin aivoatrofian sekä T1- ja T2-signaalimuutosten tilavuudet.

Tässä väestöpohjaisessa tutkimuksessa ainakin yksi NP-syndrooma todettiin 91 %:lla SLE-potilaista. Kognitiivinen häiriö oli yleisin yksittäinen syndrooma; seuraavina tulivat päänsärky ja mielialahäiriö. Kun lievät NP-syndroomat (lievä kognitiivinen häiriö, päänsärky, lievä depressio, ahdistuneisuus ja polyneuropatia ilman ENMG-vahvistusta) poissuljettiin, NPSLE:n prevalenssi laski 46 %:iin.

Kaikkia NP-syndroomia esiintyi SLE-potilailla enemmän kuin verrokeilla. Kuitenkin useimpia syndroomia oli todettavissa myös verrokeilla, minkä vuoksi luokittelun spesifisyys on heikko. Kehittääksemme kriteeristöä loimme korjatun version pohjautuen objektiivisiin löydöksiin.

Poissulkemalla lievät NP-syndroomat vain 7 %:lla kontrolleista oli todettavissa NP manifestaatio (vrt. 54 %:lla käyttäen alkuperäistä kriteeristöä).

Seerumin MMP-9-pitoisuuksissa ei ollut eroa SLE-potilaiden ja verrokeiden välillä. Kuitenkin potilasryhmän niillä potilailla, joilla oli ainakin yksi NP-syndrooma, MMP-9-pitoisuudet olivat merkittävästi korkeampia kuin niillä, joilla ei ollut NP-syndroomaa. Samoin SLE-potilailla, joilla oli todettavissa kognitiivisia häiriöitä, MMP-9-pitoisuudet olivat korkeammat kuin SLE-potilailla, joiden kognitiivinen tilanne oli normaali. Lisäksi seerumin MMP-9-pitoisuudet korreloivat positiivisesti aivojen T1- ja T2-signaalimuutosten tilavuuksiin.

Verrokkeihin verrattuna SLE-potilaiden aivojen MK:ssa oli todettavissa suuremmat T1- ja T2-signaalimuutosten sekä atrofian tilavuudet. Aivoatrofia oli yhteydessä kognitiiviseen häiriöön, epileptisiin kohtauksiin ja aivoverenkiertohäiriöihin; T1-muutokset epileptisiin kohtauksiin ja T2-muutokset kognitiiviseen häiriöön. SLE-potilaiden kumulatiivinen kortisoniannos korreloi positiivisesti aivoatrofian määrään.

Yhteenvetona, NPSLE:n prevalenssi populaatiopohjaisessa aineistossa SLE-potilaita oli 91 % käyttäen ACR:n luokittelujärjestelmää ja 46 % käyttäen korjattua kriteeristöämme, jossa poissuljettiin lievät NP-syndroomat ilman neurologista vauriota. Kognititiivinen häiriö oli yleisin NP-manifestaatio. ACR:n kriteeristö ei erotellut potilaita verrokeista. Aivojen MK:ssa atrofia, aivoverenkiertohäiriöt ja demyelinaatiomuutokset olivat yleisempiä SLE-potilailla kuin verrokeilla ja liittyivät tiettyihin NP-manifestaatioihin. Kohonneet MMP-9-pitoisuudet SLE-potilailla saattavat liittyä NP sairastavuuteen, erityisesti kognitiiviseen häiriöön.

INTRODUCTION

SLE is a chronic idiopathic autoimmune disorder with a broad spectrum of clinical and immunologic manifestations affecting multiple organ systems. A challenging problem in SLE is the diagnosis and management of NP involvement. According to the definition of NPSLE, this condition includes neurologic syndromes of the central, peripheral, and autonomic nervous system and the psychiatric syndromes observed in patients with SLE (ACR 1999). NPSLE may present with serious manifestations (eg. acute confusional state, seizure disorder, and stroke), but more subtle deficits as mild cognitive dysfunction have also been recognized (Van Dam AP 1991, Carbotte et al 1986, Hermosillo-Romo & Brey 2002). The prevalence of NPSLE has ranged widely reflecting variable diagnostic criteria and differences in selection of patients for study (McCune & Golbus 1988; Hanly & Liang 1997). A former definition for NPSLE in the 1982 revised American College of Rheumatology (ACR) criteria for SLE has been inadequate including only two elements, psychosis and seizure. The ACR has developed in 1999 a standardized nomenclature system, providing case definitions for 19 NP syndromes seen in SLE and recommendations for laboratory and imaging tests (ACR 1999).

The pathogenesis of NPSLE is still unclear, but it appears to be multifactorial and may involve autoantibody production, microangiopathy, intrathecal production of proinflammatory cytokines and atherosclerosis. The integrity of the blood-brain-barrier seems to be very important in SLE-related neuropathology. A microvasculopathy appears to be the most common microscopic brain finding in SLE (Brey 2007).

In general, the diagnosis of NPSLE is difficult, because no single laboratory marker or imaging modality serves as a gold standard, and the diagnosis is primarily clinical (Kovacs et al 1993). The assessment of patients is based on clinical neurologic and rheumatologic evaluation, immunoserological testing, brain imaging, and psychiatric and neuropsychological assessment. An important consideration is whether the particular clinical syndrome is caused by SLE-mediated organ dysfunction, a secondary phenomenon related to infection, metabolic abnormalities or medication side effects, or even by an unrelated condition (Muscal & Brey 2010).

Imaging studies are important in the management of NPSLE patients (Huizinga et al 2001; Peterson et al 2005; Castellino et al 2008). Despite many different types of brain MRI changes described in

NPSLE, no consistent pattern of abnormality has been associated with the condition (Kozora et al 1996; Tanabe & Weiner 1997). MRI abnormalities such as cortical stroke, global atrophy, non-spesific foci of increased signal in both grey and white matter on T2-weighted images, cerebral venous thrombosis, or intracranial calcifications are not specific for NPSLE (Tanabe & Weiner 1997).

MMPs are a family of endoproteinases that can degrade a variety of extracellular matrix components (Lijnen 2001). Increased activity of MMPs has been implicated in numerous disease processes, including malignancies, cardiovascular disease, and autoimmune disease such as multiple sclerosis and rheumatoid arthritis (Ahrens et al 1996; Goezl et al 1996; Lee et al 1999). The role of MMPs in the pathogenesis of NPSLE is not clear.

The aims of this study were to describe the prevalence of NP syndromes in a Finnish population of SLE patients; assess the validity of the ACR nomenclature and case definitions; investigate whether there is any association between brain atrophy and signal lesions and NP manifestations in SLE; and to evaluate whether serum MMP-9 levels are associated with NP manifestations or cerebral MRI abnormalities in SLE patients.

REVIEW OF THE LITERATURE

1. Definition and classification of SLE

SLE is a chronic relapsing-remitting autoimmune disease characterized by a wide variety of clinical manifestations. The disease occurs primarily in young women and ranges in severity from a mild disease with rash and arthritis to a illness with renal failure and profound nervous system disturbances (Pisetsky 1997). The classification of SLE is based on 11 criteria proposed by the American College of Rheumatology (ACR) and later revised (Tan et al 1982; Hochberg 1997) (Table 1).

2. Epidemiology of SLE

SLE is a worldwide disease. The incidence peaks between the ages of 15 and 40 years, with a mean age of onset in women of 32 years, and men, of 40 years (Pisetsky 1997). SLE affects multiple organ systems in women 9 times more frequently than men (Muscal et al 2010). Incidence and prevalence rates vary a lot in the world depending on genetic and possibly environmental factors. SLE is more common in African-Americans, African-Caribbeans, and Asians, than in Caucasians. Several recent studies have suggested that the incidence of SLE is increasing. However, identification of milder SLE, or earlier diagnosis of SLE could explain an apparent increase (Moss et al 2002; Petri 2002). International studies have reported prevalences of 4-250/100 000; in Finland the reported prevalence is 28/100 000 (Helve T 1985).

Table 1.
American Rheumatism Association (ARA) 1997 Revised Criteria for the Classification of Systemic Lupus erythematosus

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patients history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) Pleuritis – convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion OR b) Pericarditis
7. Renal disorder	a) Persistent proteinuria greater than 0.5 per day or greater than 3+ if quantification not performed OR b) Cellular casts
8. Neurologic disorder	a) Seizures – in the absence of offending drugs or known metabolic derangements: e.g., uremia, ketoacidosis, or electrolyte imbalance OR b) Psychosis – in the absence of offending drugs or known metabolic derangements: e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	a) Hemolytic anemia OR b) Leukopenia – less than 4000/mm total on two or more occasions OR c) Lymphopenia – less than 1500/mm on two or more occasions OR d) Thrombocytopenia – less than 100 000/mm in the absence of offending drugs
10. Immunologic disorder	a) Anti-DNA: antibody to native DNA in abnormal titer OR b) Anti-Sm: presence of antibody to Sm nuclear antigen OR c) Positive finding of antiphopsholipid antibodies
11. Antinuclear antibody	An abnormal titer of antinuclear antibody at any time and in the absence of drugs known to be associated with “drug-induced lupus syndrome”

The classification is based on 11 criteria. SLE can be diagnosed when 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

3. Clinical manifestations of SLE

General features of SLE include fatigue, fever, malaise and weight loss (Pisetsky 1997). Fatigue occurs in virtually all patients. Low-grade fever is common, it may reflect active disease or infection. Weight loss occurs in about 60% of patients (Schur 1996).

Arthritis and/or arthralgia affect 85% to 90% of patients during the course of their illness. Arthritis predominantly affects the small joints of the hands, wrists, and knees and can be deforming, although it does not produce joint erosion (Pisetsky 1997).

The skin is involved in most SLE patients. A wide variety of skin manifestations include butterfly rash, discoid rash, livedo reticularis, photosensitivity, mucous membrane lesions, alopecia and vasculitic skin lesions (Schur 1996).

Clinically evident pericarditis occurs in about 25% of patients (Rothfield 1996). Asymptomatic valvular lesions are detected by ECHO in 25% of patients, but Libman-Sacks endocarditis is now rarely seen. Occasionally it can be associated with antiphopsholipid syndrome (APS) (Pettersson et al 2005). The lung is involved in about 50% of SLE patients, with pleuritis being the most commonly noted manifestation (Schur 1996).

Renal disease is a frequent manifestation of SLE and develops in about 50%-75% of patients (Schur 1996; Pisetsky 1997). The spectrum of renal involvement is broad. Only a minority of patients develop clinical renal disease, but most patients have some histologic abnormalities of the kidneys. The basic lesion is glomerulonephritis (GN). Renal biopsy is important in assessment of the nephritis pattern and the reversibility of the lesion. The 1982 World Health Organization grading system is currently used, with Class 1 indicating a normal kidney, Class 2 mesangial GN, Class 3 focal segmental proliferative GN, Class 4 diffuse proliferative GN, Class 5 membranous GN and Class 6 chronic sclerosing GN. The higher the grade, the more severe is the renal involvement (Burnett et al 2005).

Muscle pain is a frequent complaint and accompanied on occasion by muscle wasting and weakness. True myositis is uncommon in SLE (Schur 1996).

One or more hematological abnormalities are present in nearly all SLE patients with active disease (Rothfield 1996). They may reflect the nonspecific effects of inflammation on bone marrow function as well as the binding of specific antibodies to blood cell elements. Generalized lymphadenopathy is very common, especially with active disease. Anti-phospholipid antibodies (APL) can be found in 20-35% of patients with SLE (Pisetsky 1997).

SLE may involve virtually any ocular structure. The most common ocular manifestation is xerostomia (Rosenbaum et al 1996).

Gastrointestinal symptoms are common in SLE. Complaints include dyspepsia, nausea, vomiting and abdominal pain. Etiologies include bowel vasculitis, diffuse peritonitis, pancreatitis, inflammatory bowel disease or the use of medications (Schur 1996).

The typical course of SLE is one of flares and remissions, sometimes with many months or years between periods of clinical activity. The measurement of disease activity includes monitoring certain laboratory tests and clinical features. A number of valid and reliable indices, including the SLAM (Systemic Lupus Activity Measure), SLEDAI (Systemic Lupus Erythematosus Disease Activity Index), LAI (Lupus Activity Index), BILAG (British Isles Lupus Activity Group) and ECLAM (European Consensus Lupus Activity Measure) are available for measuring disease activity in SLE and a damage index composed of variables related to irreversible organ injury from SLE and complications of therapy has been developed (Systemic Lupus International Collaborating Clinics / ACR; SLICC/ACR) (Vitali et al 1992; Gladman 1994; Caponi et al 1995).

The survival of patients with SLE has improved over the past four decades from <50% five year survival before 1955 to >90% five year survival in recent studies. The leading cause of death in patients with SLE is infection, which may be due to a complication of either active disease and/or its treatment. Other major causes of death are pulmonary, renal or CNS failure and premature coronary artery disease (Boumpas et al 1995; Schur 1996; Doria et al 2006). In a recent study patients with SLE had a death rate four times that of the general population. The most common cause of death was malignancy followed by infection and vascular disease. Early deaths were more often due to renal disease, whereas late deaths tended to be caused by atherosclerosis (Moss et al 2010).

Neuropsychiatric (NP) manifestations of SLE will be discussed later.

4. Pathogenesis of SLE

The aetiology of SLE is not known. As with most autoimmune diseases, multiple factors likely effect it. These factors include genetic predisposition, hormonal factors and environmental stimuli (Rosenbaum et al 1996).

4.1 Genetic susceptibility

SLE shows a strong familial aggregation, with a much higher frequency among first degree relatives of patients. The concordance of the disease in identical twins is approximately 25-50% and that in dizygotic twins around 5% suggesting that genetic factors play an important role in the predisposition of the disease. In a small proportion of patients a single gene may be responsible, but for most of patients multiple genes may be involved. During the past few years, linkage analyses using SLE multiplex families have provided many chromosomal regions for further exploration of susceptibility genes. It is estimated that at least four susceptibility genes are needed for the development of the disease. Population studies reveal that the susceptibility to SLE involves human leucocyte antigen (HLA) class II gene polymorphisms. An association of HLA DR2 and DR3 with SLE is a common finding in patients with different ethnicities, with a relative risk for the development of disease of approximately two to five. However, most cases of SLE are sporadic without identifiable genetic predisposing factors, suggesting that multiple environmental or yet unknown factors may also be responsible (Mok & Lau 2001; Sawalha & Harley 2004; Tsao 2004).

4.2 Role of hormones

A role of endogenous sex hormones in disease predisposition has been shown. SLE is predominantly a female disease. First flare of SLE before puberty and after menopause is uncommon. Abnormal oestrogen metabolism has been demonstrated in patients with SLE of both sexes and women with SLE also have low plasma androgens. Flares of SLE are well known to occur during periods of rapid hormonal changes. There is also evidence that endogenous oestrogen concentrations may influence disease activity and prognosis of the disease. Prolactin has been found to be an immunostimulatory hormone and hyperprolactinemia has been demonstrated in a proportion of patients with SLE of both sexes. Hormones may not have a direct causative role in

SLE, but a milieu consisting of different hormones may create an endogenous environment for susceptible individuals to develop the disease (Mok & Lau 2001).

4.3 Environmental triggers

Although genetic factors and the hormonal milieu may create a predisposition towards SLE, the initiation of the disease probably results from several environmental triggers and exogenous factors. Environmental triggers that may be relevant in the pathogenesis of SLE are chemical and physical factors, like drugs (including procainamide, hydralazine, isoniazid, quinidine, methyl DOPA and chlorpromazine), tobacco smoke, hair dyes, aromatic amines, hydrazines and UV light. Some dietary factors, like high intake of saturated fats have been suspected to precipitate SLE. Infectious agents such as viruses might theoretically initiate or cause a flare in SLE by activating B cells, damaging tissues to release autoantigens, and triggering the disease by molecular mimicry. Thus, there is little evidence to support that one infectious agent causes SLE. Viruses suspected to be involved in pathogenesis of SLE are Epstein-Barr virus, cytomegalovirus, parvovirus B19 and the retroviruses. Hormones and environmental oestrogens have been linked to autoimmune disorders. Hormonal replacement therapy and oral contraceptive pills have been associated with a small increase in the risk of SLE development (Mongey et al 1996; Mok & Lau 2001, Manson & Isenberg 2003).

4.4 Immunopathology

Multiple immunologic abnormalities are important for the development and clinical expression of SLE (Anolik & Sanz 2004). The basic pathological features are that of inflammation and blood vessel abnormalities, which include vasculopathy, vasculitis, and immune complex deposition (Mok & Lau 2001). The fundamental disturbance appears to be a dysfunction of immune system, with a loss of self-tolerance caused by alterations in B-cell functions. The disease is characterized by autoantibody production and immune-complex-mediated end-organ damage; both of them reflect the failure of immune tolerance (Burnett et al 2005; Tieng et al 2007).

The central immunological disturbance in patients with SLE is autoantibody production by B cells that normally should be inactive or tolerant and unable to produce antibodies against themselves.

There is evidence that depending on genetic background and specific environmental insults, the disease may be induced by a breakdown of B-cell tolerance leading to the generation of pathogenic antibodies (Anolik & Sanz 2004). Antibodies are directed against several self molecules found in the nucleus, cytoplasm, and cell surface. In addition to be used in diagnosis of SLE, various autoantibodies may predict the disease manifestations and be helpful in monitoring the disease activity and response to treatment (Sawalha & Harley 2004).

Antinuclear antibodies (ANA) are most characteristic and present in more than 95% of patients, making the ANA test most sensitive test for SLE (Manson & Isenberg 2003; Mok & Lau 2001; Sawalha & Harley 2004). However, ANA are not specific, because they can be detected in a variety of autoimmune, rheumatic, and infectious conditions; and even in normal individuals. The absence of ANA makes the diagnosis of SLE less likely, although still possible. The recent demonstration that patients with SLE may express ANA several years before the onset of clinical disease suggests that the breakdown of B-cell tolerance occurs very early in SLE and may precede or even trigger other immune malfunctions (Anolik & Sanz 2004; Sawalha & Harley 2004; Doria et al 2008). The antibodies with the highest specificity for the diagnosis of SLE are those directed toward dsDNA (Anti-dsDNA) (Mok & Lau 2001; Manson & Isenberg 2003). Anti-dsDNA is not particularly sensitive because it may be transiently present and found in only 50% to 60% of SLE patients at some point in their disease course. Anti-Sm antibodies are also unique to patients with SLE. The Sm antigen is designated as a small nuclear ribonucleoprotein (snRNP) (Sawalha et al 2004, Mok et al 2005). The most remarkable feature of anti-dsDNA antibodies is their association with glomerulonephritis. Raised anti-dsDNA antibody titres have been found in active lupus nephritis. Anti-dsDNA antibodies show preferential deposition in the kidneys, suggesting that DNA-anti-DNA antibody immune complexes are the main mediators of inflammation. The pathogenesis of manifestations other than glomerulonephritis is less well understood, although immune complex deposition with activation of complement at relevant sites is a probable mechanism. Anti-dsDNA antibody titers and disease activity frequently vary over time but anti Sm antibody titres remain usually constant. In addition to these antibodies, a variety of other autoantibodies are often detected. The antigens targeted may be associated with patient ethnicity or particular disease manifestations (Manson & Isenberg 2003) (Table 2).

The mechanisms by which B cells may influence SLE are diverse and include in addition to autoantibody-dependent functions also autoantibody–independent ones. B cells act as antigen-presenting cells and provide costimulatory signals necessary for T-cell activation, differentiation,

and expansion. B-cells also respond to or secrete cytokines such as interleukin (IL)-10,IL-6, tumor necrosis factor (TNF)-alfa and interferon (IFN)-alfa. Furthermore, they link innate and acquired immunity by Toll-like receptors and affect follicular dendritic cell differentiation. Alterations in one or more B-cell functions can lead to a breach of tolerance and to the development of autoimmune disease (Anolik & Sanz 2004; Tieng 2008).

Abnormalities in T cell function are also evident in patients with SLE. The number of activated T cells has been found to be increased in peripheral blood in SLE patients. The activated T cells are able to stimulate the B cells to produce autoantibodies (Mok & Lau 2001; Hoffman 2004; Kyttaris et al 2004). The propagation of self-directed B-cell clones may also be assisted by an inappropriate lack of T-cell suppression (Manson & Isenberg 2003).

Cytokines are low-molecular-weight proteins which act as the chemical modulators of the immune system. Cytokine profiles in patients with SLE have been studied extensively. Interleukin-10 (Il-10) is secreted by T-helper cells, and stimulates B-cell proliferation and antibody production. The serum concentrations of IL-10 are significantly higher in SLE patients than in controls. There is an increasing body of research to suggest that this cytokine may be central to the overproduction of antibody seen in SLE (Mok & Lau 2001; Manson & Isenberg 2003). Tumour necrosis factor α (TNFα) has also been investigated, and there is some evidence suggesting that it may be protective against SLE (Manson & Isenberg 2003).

The clearing of immune complexes by phagocytic cells is defective in patients with SLE and this has been considered to be an important pathogenetic mechanism in SLE. Complement is involved in the clearance of immune complexes. Genetic complement deficiencies have been found in SLE patients and complement consumption, with falling serum concentrations, often mirrors disease activity (Mok & Lau 2001; Manson & Isenberg 2003).

The understanding of autoimmune diseases has increased since the Toll-like receptors (TLRs) have been identified as possible key players in autoimmune pathophysiology. These receptors are transmembrane proteins that are expressed in various immune cells such as B-cells, macrophages and specific types of T-cells. They recognize a variety of structures derived from viruses, bacteria and fungi, so called pathogen-associated molecular patterns (PAMPs) and also endogenous danger signals named alarmins, leading to subsequent initiation of relevant immune responses, rapid and effective control of infection. In addition TLRs may be involved in the induction of chronic

inflammation and autoimmune reactions. Endogenous ligand such as RNA and DNA can activate TLRs under certain conditions and induce a typical autoimmune reaction. The resulting cytokine production after TLR activation may trigger and continue the autoimmune process (Hurst et al 2008; Pöllänen et al 2009).

Flares of SLE are accompanied by a diffuse vasculopathy in which the endothelium is activated. Adhesion molecules, expressed on vascular endothelium and circulating leucocytes, regulate the processes by which leucocytes bind to and migrate through endothelium, and mediate a number of central cellular interactions in inflammatory responses. Vascular cell adhesion molecule-1 (VCAM-I) upregulation has been reported in patients with active SLE in several studies (Merrill et al 2005).

Table 2. Common antinuclear antibodies in SLE (Sawalha & Harley 2004).

Autoantibody	Frequency (%)	Autoantigen
Anti-dsDNA	50-60	DNA double helix
Anti-Sm	10-25	Spliceosomal snRNP
Anti-Ro (SS-A)	25-40	60-kDa or 52-kDa proteins
Anti-La (SS-B)	10-15	48-kDa proteins
Anti-Ribosomal P	15	Ribosomal phosphoproteins P0, P1, P2
Anti-nRNP	23-40	Spliceosomal snRNP
Anti-Histone	50-70	H1, H2A, H2B, H3, H4, H5
Anti-Ku	20-40	p70/80 proteins

dsDNA, double-stranded DNA; Sm, Smith; snRNP, small nuclear ribonucleoprotein; nRNP, nuclear ribonucleoprotein

4.5 Apoptosis

Evidence is accumulating that implicates apoptosis, programmed cell death, as a mechanism by which SLE may be provoked and propagated. Precipitating factors such as UV light, infections and drugs may cause increased apoptosis. This can result in increased exposure of target antigens and production of antibodies. Under normal circumstances, apoptotic cells are engulfed by macrophages in the early phase of apoptotic cell death without inducing inflammation or the immune response. Recent studies have shown that the clearance of apoptotic cells in patients with SLE is impaired. The reasons are not clear. It could be the result of defects of early complement proteins, such as C2, C4, or C1q. Patients with homozygous deficiencies in these complement components develop a severe lupus-like disease early in life (Mok & Lau 2001; Manson & Isenberg 2003). High concentrations of plasma membrane-derived vesicles also known as microparticles have also been suspected. They are small membrane-bound vesicles which are able to reduce phagocytosis of apoptotic cells. In SLE, there have been measured raised levels of microparticles (Antwi-Baffour et al 2010).

5. Definition and classification of neuropsychiatric SLE (NPSLE)

NPSLE includes the neurologic syndromes of the central, peripheral, and autonomic nervous system observed in patients with SLE. It is estimated that two thirds of NP manifestations in SLE are not directly related to active NPSLE (primary NPSLE) but instead are a consequence of secondary causes such as drugs, infections, and hypertensive and metabolic complications (secondary NPSLE). The NP symptoms vary in their clinical expression from focal to diffuse manifestations (Kovacs et al 1993). They can also be divided to major symptoms, including eg. cerebrovascular events, seizures and psychosis; and minor symptoms eg. headaches, mood swings and cognitive complaints (Denburg et al 1993). There is no single diagnostic test sensitive and spesific for NPSLE. The assessment of individual patients is based on clinical neurological and rheumatological evaluation, immunoserological testing, brain imaging, and psychiatric and neuropsychological assessment (Brey 2007). NPSLE syndromes can occur as a single event, or multiple events at any time during the course of the disease, even during periods in which no disease activity is detected outside the nervous system. Approximately 28% to 40% of the NPSLE manifestations develop before the onset of SLE, or at the time of diagnosis, and 63% within the first year after diagnosis

(Brey 2007; Burnett et al 2005). NPSLE has been reported to be a prognostic factor for a poor long-term outcome in SLE. In a recent study, the occurrence of NP events in newly diagnosed patients was associated with reduced quality of life and increased organ damage (Hanly et al 2007). The mortality rate in NPSLE has varied from 7% to 40% depending on the particular manifestation, and NP involvement constitutes the second most common cause of death in SLE after renal failure (Kovacs et al 1993; Sibbitt et al 1999)

Central nervous system involvement in SLE was first described by Kaposi in 1872; recurrent stupor and coma were noted in two of his original patients with SLE (Feinglass et al 1976; Ellis & Verity 1979). The systemic nature of the illness was first emphasized by Osler; among the 29 patients whom he described between 1895 and 1903, there were two with neurologic or psychiatric manifestations. One of these cases presented with delirium and the other with five or six episodes of aphasia and hemiplegia (Feinglass et al 1976; Futrell et al 1989). The clinical spectrum of NP manifestations in SLE was clarified by Harvey et al and Dubois et al. In Harvey`s monograph in 1954, 37% of 105 patients with SLE developed nervous system involvement. Dubois reported a large serie, 520 SLE patients with CNS involvement occuring in 25%; NP abnormalities were a frequent cause of death (Harvey et al 195; Dubois & Tuffanelli 1964).

Since those decades, NP manifestations in SLE have been a subject of several studies. Johnson and Richardson reported a 75% incidence of CNS involvement in a retrospective autopsy series (Small et al 1977). Estes and Christian followed the progress of 150 patients with SLE for up to 8 years; 59% developed a neurologic disease. Feinglass et al evaluated retrospectively 140 hospitalized patients with SLE; NP features were found in 51% of them. In both of these studies, psychiatric disorders and epileptic seizures were the most frequent manifestations (Estes & Christian 1971; Feinglass et al 1976) In general, the reported prevalence of NP manifestations in SLE in the last century has varied widely, from 14% to 75%, though most clinical studies agreed that NP involvement occurs in approximately 50% of SLE patients (Estes & Christian 1971; Feinglass et al 1976; Gibson & Myers 1976; Grigor et al 1977; Tan et al 1978; Abel et al 1980).

The most important explanation for the variability in the prevalence of NPSLE is that the definition and nomenclature of NPSLE has not been standardized (ACR 1999). Different investigators have used markedly different terminology, making cross-study comparisons and conclusions difficult (Sibbitt et al 1999). It has been even claimed, that the literature describing NP syndromes is a phenomenological nightmare (Calabrese et al 1995). Neurologic and psychiatric manifestations

have been termed *CNS vasculitis, CNS lupus, neurolupus, neuropsychiatric lupus*, or *lupus cerebritis*. In older studies, the diagnosis of NPSLE has been made on the basis of major NP involvement. Since then there has been increasing awareness also of minor manifestations, especially of cognitive impairment due largely to the application of standardized neuropsychological assessment techniques. A former definition for NPSLE in the 1997 revised ACR criteria for SLE is inadequate because only two elements, psychosis and seizures, were included (Table 1).

In 1999, ACR developed a standardized nomenclature system providing case definitions for the NP syndromes of SLE to facilitate and enhance patient classification and reporting requirements in clinical research. The committee consisted of 35 international members representing rheumatology, neurology, psychiatry, neuropsychiatry and haematology. It developed 19 NPSLE case definitions with diagnostic criteria, exclusions, associations and ascertainment, as well as reporting standards (Table 3.). Recommendations were also included for minimum laboratory evaluation and imaging techniques. ACR eliminated the term lupus cerebritis because true cerebral vasculitis is rarely found in SLE despite its popular use as a clinical diagnosis. Similarly, because both psychiatric and peripheral nervous system disorders may be present, the term CNS lupus was considered inappropriate. The term NPSLE was recommended to describe the wide range of psychiatric and neurologic syndromes in SLE (ACR 1999).

Published experience with the ACR nomenclature and case definitions

Studies using the ACR case definitions have detected the presence of 14 to 17 of the 19 syndromes and reported a fairly consistent prevalence of the following syndromes: headache (39%-61%), seizures (8%-18%), cerebrovascular disease (2%-8%), psychosis (3%-5%), cranial neuropathy (1.5%-2.1%) and movement disorder (1%). The range in the prevalence of cognitive dysfunction was much wider, with studies using systematic assessment of cognitive function finding a higher prevalence (75%-80%) than studies that evaluated patients using sensitive instruments only if clinically indicated (5.4%). Accordingly, mood disorders were found from 12.4 % to 69%-74% of patients depending whether sensitive psychiatric assessments were used or not (Muscal & Brey 2010).

In the San Antonio Lupus Study of Neuropsychiatric disease, 128 unselected subjects with SLE were evaluated and one or more NPSLE syndromes were found in 80% of these patients The most

common manifestations were headaches in 57%, major depressive-like episodes in 28%, anxiety disorder in 24% and mood disorder with depressive features in 19% (Brey et al 2002). In another study using ACR case definitions the prevalence of NPSLE was 72%. Cognitive dysfunction in 52% of patients was followed by mood disorders (27%), cerebrovascular disease (24%) and headache (21%) (Afeltra et al 2003). A retrospective application of the ACR case definitions on 527 SLE patients classified 39 patients with seizures, 28 with psychosis, 20 with polyneuropathy, 15 with acute confusional state and 13 with cerebrovascular disease (Costallat et al 2001). In another retrospective study, 185 out of 323 consecutive patients with SLE had NP manifestations according to ACR case definitions (Sanna et al 2003). In a recent international inception cohort study, 28% of SLE patients experienced at least 1 NP event around the time of diagnosis of SLE, of which only a minority were attributed to SLE (Hanly et al 2007).

In an international multicentre study, 1206 patients with SLE were evaluated prospectively with a mean follow-up of 23 months. 40.3% of patients had at least one NP event, which weas attributed to SLE in 13-24% of patients. The most common events were headache (47%), mood disorders (17%) and seizures (8%). Formal neuropsychological assessments were not performed on all patients and neuroimaging studies were done only if clinically indicated (Hanly et al 2010).

Table 3. The neuropsychiatric syndromes in SLE according to the American College of Rheumatology nomenclature and case definitions (ACR Ad Hoc Committee on neuropsychiatric Lupus Nomenclature 1999).

Central nervous system	*Peripheral nervous system*
Aseptic meningitis	Acute inflammatory demyelinating polyradiculoneuropathy
Cerebrovascular disease	
Demyelinating syndrome	Autonomic disorder
Headache	Mononeuropathy, single/multiplex
Movement disorder (chorea)	Myasthenia gravis
Myelopathy	Neuropathy, cranial
Seizure disorders	Plexopathy
Acute confusional state	Polyneuropathy
Anxiety disorder	
Cognitive dysfunction	
Mood disorder	
Psychosis	

6. Clinical features of NPSLE

6.1 Central nervous system

6.1.1. Aseptic meningitis

The term aseptic meningitis is used for a meningeal syndrome of non-infectious origin with some degree of nuchal rigidity and pleocytosis in the cerebrospinal fluid (CSF). Aseptic meningitis is one of the least common manifestations of NPSLE. It can be the initial symptom of SLE and may occur early in the course of illness. Aseptic meningitis in SLE is probably heterogeneous in origin and due to vasculitis in some cases. The deposition of immune complexes in the choroid plexus has been suspected in pathogenesis. When making a diagnosis of aseptic meningitis as a part of active SLE, nonsteroidal anti-inflammatory drugs (NSAID) as a potential cause must be excluded. Aseptic meningitis as a side effect of NSAID is probably more common in SLE patients than in others (Kovacs et al 1993; Ostensen & Villiger 2001; Jennekens & Kater 2002).

According to the ACR case definitions, acute or subacute onset of headache with photophobia, neck stiffness, and fever; signs of meningeal irritation; and abnormal CSF should be observed to make a diagnosis of aseptic meningitis (ACR 1999).

6.1.2. Cerebrovascular disease

Stroke occurs in patients with SLE via a variety of mechanisms, including cardiogenic embolus, large-vessel occlusion or stenosis, small-vessel ischemia, and intracranial hemorrhage. It is not known how often stroke in SLE is due to cerebral venous thrombosis. Stroke due to vasculitis is probably rare. Ischaemic stroke in SLE is attributed at least in part to circulating antiphospholipid antibodies and premature atherosclerosis (Jennekens & Kater 2002).

Stroke is among the CNS diagnoses in all large series of patients with SLE (Estes & Christian 1971; Feinglass et al 1976; Tan et al 1978, Abel 1980; How et al 1985; Futrell et al 1989; Sibley et al 1992). The estimated frequency of strokes and transient ischemic attacks (TIA) among SLE patients ranges from 3% to 19% (Estes & Christian 1971; Feinglass et al 1976; Gibson & Myers 1976; Grigor et al 1978; How et al 1985; Futrell & Millikan 1989). Futrell and Millikan reviewed 105

patients with SLE and found that the majority of patients had their first cerebrovascular accident within the first 5 years of illness and the mean age at the time of stroke was 40 years (Futrell & Millikan 1989). SLE patients with a history of cerebral infarct or TIA are at a high risk for recurrent cerebral ischemia, the risk may be over 50% (Kovacs et al 1993).

The ACR case definitions suggests the following diagnostic criteria for cerebrovascular disease: stroke syndrome, TIA, chronic multifocal disease, subarachnoid and intracranial hemorrhage and sinus thrombosis; supporting radioimaging study must be included and antiphospholipid antibodies (APL) recorded (ACR 1999). In newer studies using ACR case definitions the prevalence of cerebrovascular disease has varied from 2% to 24% (Brey et al 2002; Sanna et al 2002; Afeltra et al 2003; Hanly et al 2004)

6.1.3. Demyelinating syndrome

The term “lupoid sclerosis” has been used to describe SLE patients with complex neurologic deficits similar to those seen in multiple sclerosis (MS). This particular syndrome might represent a concordance or overlap of two autoimmune conditions. It often refers to relapsing myelopathy or optic neuropathy in patients whose laboratory abnormalities support the diagnosis of SLE. (ACR 1999; Jennekens & Kater 2002; Hanly et al 2005). In CSF oligoclonal bands may exist and multifocal white matter bright spots may be seen on magnetic resonance imaging (MRI) studies. A Finnish epidemiologic survey found three instances of both MS and SLE occuring in the same patients (Kinnunen et al 1993). To facilitate further research, the ACR case definitions recommend the term demyelinating syndrome to be used instead of lupoid sclerosis (ACR 1999).

6.1.4. Headache

Head pain or headache is a common symptom both in SLE patients and in the normal population; whether there is a unique syndrome attributable to SLE is debated (Liang & Karlson 1984; ACR 1999, Hanly et al 2005). A large number of studies have reported the prevalence of headache in SLE ranging from 30% to 65% (Mitsikostas et al 2004). Isenberg et al published the first controlled trial on this subject. They found that migraine with aura was more prevalent in SLE patients than in

controls, suggesting that migrainous phenomena may be a feature of SLE (Isenberg et al 1982). The incidence of migraine was prospectively studied in 90 patients and controls by Markus & Hopkinson; a history of migraine in SLE patient group (34%) was approximately twice as common as in controls. An association between migraine and SLE disease activity was found, too (Markus & Hopkinson 1992). In another study, the overall prevalence of headache, tension-type headache, and migraine was similar among patients and controls (Fernandez-Nebro et al 1999).

In two recent controlled studies the prevalence of headache in SLE has been investigated. In the first one, migraine was significantly more prevalent among SLE patients than in patients with rheumatoid arthritis (RA), and related with SLE activity and organ damage measured by SLICC (Appenzeller & Costallat 2004). In another study, headaches were also more prevalent in SLE patients than in RA patients, but no particular primary headache type reached significant difference between the two groups. The scores for SLE activity or damage, function disability and quality of life were similar between SLE headache suffers and SLE headache-free patients (Weder-Cisneros et al 2004). Both studies agreed that Raynaud`s phenomenon is associated either with migraine or headache in general in SLE patients.

Although there is a serious doubt about relationship between headache and SLE, all the following entities are included in the ACR case definitions: migraine without aura, migraine with aura, tension headache, cluster headache, headache from intracranial hypertension and intractable, nonspecific headache (ACR 1999).

6.1.5. Movement disorder (chorea)

Although a number of movement disorders have been reported in patients with SLE, the ACR case definitions accepted only chorea, which is the most common of these disorders (ACR 1999). It is recognized in less than 2% of cases and tends to appear early in the course of illness and resolve regardless of treatment (Kovacs et al 1993). It may be unilateral or generalized and is often accompanied by other focal neurologic signs or by changes in mental status. APLs are present in many SLE patients with chorea. The imaging features and histopathological studies point to abnormalities of the basal ganglia, but it is not yet clear whether chorea is due to vascular insult or to antibody-induced neuronal dysfunction (Jennekens & Kater 2002).

6.1.6. Myelopathy

Spinal cord disease is a rare but well-described complication in SLE. Transverse myelitis occurs in under 1% of patients with SLE and is characterized by the development of paraplegia, associated with back pain and sensory loss. It is usually seen in late course of the illness and carries a poor prognosis. Vasculitis is a prominent feature of the spinal cord on post-mortem. There has been an association with APL suggesting that the symptom might result from a coagulopathy or that antibodies cross-react with spinal cord phopsholipids. At least 25% of patients with myelopathy develop optic neuropathy, usually bilateral (Devic`syndrome). Secondary causes of myelopathy in SLE include an epidural or paraspinal abscess, epidural or subdural hematoma, disc herniation, and intramedullary or extramedullary tumor (Kovacs et al 1993; Liang et al 1994; Brey 2000; Jennekens & Kater 2002).

6.1.7. Seizure disorders

Seizures are part of the revised ACR classification criteria for SLE. They have been reported in 8% to 35% of patients with SLE, although fatal status epilepticus is rare. Seizures are usually generalized, but focal seizures have also been reported (McCune et al 1988; Kovacs et al 1993; Brey et al 2002, Sanna et al 2002). They may antedate a diagnosis of SLE by years or be the first manifestation of the disease (Liang & Karlson 1996). APLs have been reported with increased frequency in SLE patients with epilepsy. The aetiology of seizures may be an APL-associated cerebral infarction (Brey 2000). In a study of 519 patients, 60 (11.7%) patients with epileptic seizures were identified and all seven patients who presented recurrent seizures had antiphospholipid syndrome (Appenzeller et al 2004). The differential diagnosis of seizures in SLE patients includes pre-existing seizure disorders unrelated to SLE or seizures secondary to other manifestations of SLE, such as uremia, hypertension, stroke or infection (Kovacs et al 1993; Ranua 2005).

6.1.8. Acute confusional state

In the literature, the term organic brain syndrome is commonly used to define disturbed mental functioning with delirium, emotional inadequacy, impaired memory or concentration, incoherent speech, and increased or decreased psychomotor activity in the absence of any secundary causes (Kovacs et al 1993). The incidence of organic brain syndrome has varied between 2-35% (Estes & Christian 1971; Grigor et al 1978; How et al 1985; van Dam 1991). The disturbances typically develop over hours to days and tend to fluctuate during the course of the day (ACR 1999). Metabolic abnormalities such as hypoxia and electrolyte abnormalities should be sought after and corrected and CNS infection and hypertensive encephalopathy should be excluded (Liang & Karlson 1996; Hanly et al 2005).

The term “acute confusional state” is equivalent to the term “delirium”, and according to the ACR nomenclature it should be used instead of the term “organic brain syndrome”. Diagnostic criteria for this statement are disturbance of consciousness or level of arousal and acute or subacute change in cognition and/or a change in behavior, mood, or affect. If only cognitive deficits are present, and not the other features, the syndrome should be diagnosed as “cognitive dysfunction” (ACR 1999).

6.1.9. Anxiety disorder, mood disorder and psychosis

In older literature, reported frequencies of psychiatric symptoms have varied between 3 and 82%. Variations might be caused by the way data were collected, by in- or exclusion of mild or functional complaints as symptoms of NPSLE and by the profession of the investigator; psychiatrists and psychologists tended to report more psychiatric disease if compared to other physicians (Estes & Christian 1971; Feinglass et al 1976; Gibson & Myers 1976; Grigor et al 1978; How et al 1985; van Dam 1994).

A case of SLE psychosis may present with paranoia and visual and auditory hallucinations. Recovery is complete but relapses are common (Sibley et al 1992). The incidence of psychosis in SLE is not easy to estimate reliably because the literature often fails to distinguish psychosis from acute confusional state and because the distinction from corticosteroid psychosis is difficult (Jennekens & Kater 2002).

Psychiatric manifestations often occur in the absence of SLE disease activity, are more likely to occur in patients with past NPSLE episodes, and can be exacerbated by recent stressful life events in patients with clinically mild disease activity. The debate in the literature is whether psychiatric features are a reflection of active disease or a simply a consequence of emotional stresses that accompany a chronic, painful, and sometimes debilitating disease (Hay 1992; Hermosillo-Romo et al 2002). In some studies noted association between antiribosomal P protein antibodies and psychosis and APL and depression supports an organic basis for this presentation (Bonfa et al 1987; Arnett et al 1996; Hermosillo-Romo et al 2002). Despite the controversy over milder psychiatric complaints being features of NPSLE anxiety disorder, mood disorder and psychosis are involved in the ACR case definitions (ACR 1999).

6.1.10. **Cognitive dysfunction**

The prevalence of cognitive abnormalities in SLE patients has varied widely from 21-66% most probably due to differences in patient selection and case-definition. Very different sets of neuropsychological tests have been used and different criteria for defining impairment have been adopted. In these studies, consecutive clinical samples are composed of very different proportions of active, inactive, and never NPSLE patients (Carbotte et al 1986; Denburg et al 1993; Hanly et al 1998; Denburg et al 2003). Many patients with SLE have a host of comorbidities (eg psychiatric) and other potentially confounding factors (Hermosillo-Romo et al 2002). However, the important consistent finding in these studies has been that cognitive impairment is significantly more frequent in SLE patients than in matched samples of healthy subjects or other patients with systemic disease. In addition, throughout the studies, subclinical cognitive impairment has been detected. Even in the absence of overt NP symptoms, a sizable proportion of SLE patients have been shown to have significant cognitive problems. Although a stable feature of CNS involvement in many patients with SLE, cognitive dysfunction fluctuates over time, transiently approaching the dementia severity range in a small number of patients. (Denburg et al 1993; Carbotte et al 1995; Hanly et al 1998; Hermosillo-Romo et al 2002; Denburg et al 2003). No pattern of cognitive dysfunction has emerged to be spesific for SLE, but most studies have reported deficits in attention and concentration, decreased psychomotor speed, mild verbal memory problems, decreased verbal fluency, and executive dysfunction (Denburg et al 1993; Hanly et al 1998). Studies using ACR case definitions have detected the total range of cognitive disorders to be between 52%-78% when cognitive function is tested in every patient by neuropsychological instruments. Remarkably lower prevalence

rates (5%-11%) have been found in studies that evaluated patients using sensitive instruments only if clinically indicated (Brey et al 2002; Sanna et al 2002; Afeltra et al 2003; Hanly et al 2007).

Cognitive impairment in SLE patients is assumed to reflect CNS dysfunction. Two possible causes of cognitive disorder have been suggested; small-vessel vasculopathy and an antibody-mediated effect on neuronal functioning (Denburg et al 1993; Denburg et al 2003; Hanly 2004). In a cross-sectional assessment of cognitive and APL status in 118 consecutive adult SLE patients, LA-positivity was associated with an almost two-fold increased risk of cognitive impairment (Denburg et al 2003). Denburg has also reported associations of neuronal antibodies and lymphocytotoxic antibodies with cognitive functioning (Denburg et al 1987; Denburg et al 2003). Several studies have examined the association between cognitive dysfunction and other clinical features. Most studies have found no association between disease activity and cognitive disordes. The presence of other overt NP manifestations at any time in the disease course or at the time of neuropsychological testing is frequently linked with impaired cognitive performance. Comorbid psychiatric disorders can be found in up to 40% of patients with SLE who have cognitive dysfunction and changes in psychiatric disorders have been shown to parallel changes in cognitive function. Hippocampal atrophy has shown to be a negative prognostic factor to cognitive dysfunction and a progression of atrophy a predictor of progressive cognitive impairment. Controversy exists about the role of corticosteroid use beyond the cognitive dysfunction, most cross-sectional studies report no association between cognitive dysfunction and the use or dose of corticosteroid. An association between cognitive dysfunction and various chemotherapeutic drugs in several cancer populations has been found. Similarly, alkylating agents, such as cyclophospamide may have an effect on cognitive function in SLE patients (Denburg et al 1993; Ginsburg et al 1992; Hay et al 1992; Fisk et al 1993; Carbotte et al 1995; Hanly et al 1998; Hermosillo-Romo et al 2002; Hanly et al 2005; Appenzeller et al 2006).

Cognitive impairment is most reliably detected and monitored by neuropsychological examination. The use of standardized tests for screening cognitive function such as the Mini-Mental State Examination is limited with substantial rates of false-negative findings. According to the ACR nomenclature, the diagnostic criteria for cognitive dysfunction require documentation by neuropsychological testing (documented impairment in one or more of the cognitive domains: simple attention, complex attention, memory, visual-spatial processing, language, reasoning/problem solving, psychomotor speed and executive functions); and a significant decline from a former level of functioning (ACR 1999).

6.2 Peripheral nervous system

Manifestations resulted from peripheral nervous system (PNS) involvement have not been extensively investigated in SLE. The reported frequencies of abnormalities in PNS have mostly varied between 2% and 27%, but when evaluated using clinical electromyography and nerve conduction velocity studies, clinical and subclinical peripheral nerve abnormalities are detected in up to 47% of unselected SLE patients (Estes & Christian 1971; Feinglass et al 1976, Gibson & Myers 1976; Grigor et al 1978; Omdal et al 1988; Hermosillo-Romo et al 2002). A mild, symmetric distal sensory or sensomotor neuropathy is the most common peripheral neuropathy in SLE. Usually, the neuropathic process is modestly progressive over time, but it may fluctuate and is not necessarily irreversible (Goransson et al 2006). In most patients, biopsy and electrodiagnostic findings would be consistent with vasculitic neuropathy (Rosenbaum et al 1996). Peripheral neuropathy has been linked to cutaneous vasculitis and renal failure. It may be an important prognostic factor for mortality in SLE (Hermosillo-Romo et al 2002).

Some patients with SLE have neuropathic symptoms despite normal results of clinical evaluation and nerve conduction studies. Since small nerve fibers convey perceptions of warmth and burning pain (C fibers) and cold and sharp pain (A alfa fibers), a pure small-diameter nerve fiber neuropathy may be responsible for this. The optimal method for proving the diagnosis of small fiber neuropathy is not established; measurement of warmth-detection thresholds or heat-pain thresholds and quantitative estimation of epidermal nerve fibers have been used. (Omdal et al 2002; Goransson et al 2006)

Acute ascending paralysis (the Guillan-Barre syndrome) has reported to occur in less than 1% of patients; chronic inflammatory demyelinating polyneuropathy has also been linked to SLE.

Mononeuritis multiplex in SLE is quite rare and almost always accompanied by evidence of active disease in other organs, although occasionally it may be the presenting feature of the disease (Martinez-Taboada et al 1996).

Carpal tunnel syndrome may be the most common peripheral nerve complication of SLE.

Cranial nerve syndromes have been reported in 3-16% of SLE patients in several large series (Estes & Christian 1971; Feinglass et al 1976; Gibson & Myers 1976; Grigor et al 1978). Most often described neuropathies have related to the function of the eye (Kovacs et al 1993). Optic neuropathy occurs in about 1% of patients, in some cases associated with myelopathy but often without such an association. No particular clinical pattern predominates; visual loss, pain and visual field defects may appear. Vascular origin; small vessel disease or vasculitis, have been suggested as an ethiology for optic neuropathy in SLE. Other cranial nerve disorders seen in SLE include trigeminal neuralgia and facial neuropathy (Rosenbaum et al 1996, Jennekens & Kater 2002).

Myasthenia gravis is an autoimmune disorder mediated by antibodies to acetylcholine receptors. It may occur with other disease of immunologic origin and has been diagnosed in patients with SLE but is rare (Rosenbaum et al 1996; ACR 1999).

7. Pathogenesis of NPSLE

The origin of NP manifestations in SLE has remained unresolved, but some progress has been noted. NPSLE is a heterogeneous disorder and it is unlikely that a single mechanism will account for the diversity of features seen (Kovacs et al 1993; Trysberg & Tarkowski 2004; Brey 2007). APL-mediated ischemia, microthrombosis and noninflammatory vasculopathy, local production of cytokines leading to neuronal cytotoxicity, and direct interaction of autoantibodies with autoantigens on neuronal cell membranes, leading to interference with neurotransmission, loss of neuronal plasticity, and neuronal cell death may be involved in the pathogenesis (Hermosillo-Romo et al 2002; Senecal & Raymond 2004; Trysberg & Tarkowski 2004). It is becoming clearer that the integrity of the blood-brain-barrier is very important in SLE-related neuropathology. It is possible that the magnitude and degree of dysfunction of the blood-brain-barrier in concert with the type and level of autoantibodies may be the determining factor regarding their pathogenicity in the brain (Brey 2007; Muscal & Brey 2010). In general, inflammatory disorders are no longer considered to be the main cause of damage, instead current knowledge holds ischaemia to be the main reason for NP manifestations (Hermosillo-Romo et al 2002; Jennekens & Kater 2002; Trysberg & Tarkowski 2004).

One way to categorize the mechanisms of clinical injury is to distinguish immunologic effects directly affecting nervous system cells (neurons, glial cells, ependyma) from secondary ischemic effects caused by immune-mediated injury on vascular tissue. Table 4 summarizes the immunopathogenic mechanisms of NPSLE (Moore & Lisak 1995).

Table 4. Immunopathogenesis of NPSLE (Moore & Lisak 1995).

Primary	Immune-mediated *direct* effects	
		Immune complexes
		Autoantibodies
		Cytokines
		Activated lymhocytes
	Immune-mediated *indirect* effects	
		Vasculopathy
		Coagulopathy
		Emboli from cardiac disease
		Hematologic disturbances
Secondary	Infectious	
	Metabolic	
	Toxic	

7.1. Direct immune-mediated effects

Immune-mediated direct effects result from the action of antibodies, cytokines, or immune complexes on neurons or, possibly, glia. Typically these effects are acute or subacute in onset (Moore & Lisak 1995).

7.1.1. Autoantibodies

Although autoantibodies have long been considered as primary suspects, their role in pathogenesis of has not been established (Senecal & Raymond 2004; Brey 2007). The evidence based on human studies of the importance of them is largely circumstantial, and includes a temporal relationship between autoantibodies and NP manifestations, their presence in both CSF and serum, and their detection in neuronal tissues of some patients succumbing to NP manifestation (Hanly 1998).

The integrity of the blood-brain barrier seems to be very important in SLE-related neuropathology. An abnormal endothelial-white blood cell interaction, allowing proteins or cells to access to the CNS, may be a mechanism whereby autoantibody-mediated CNS effects can occur. This can be stimulated by proinflammatory cytokines or certain autoantibodies (Brey 2007). Direct interaction of autoantibodies with autoantigens on neuronal cell membranes may lead to interference with neurotransmission, loss of neuronal plasticity, and neuronal cell death (Senecal & Raymond 2004).

Table 5 lists most common autoantibodies reported in NPSLE and associated clinical manifestations (Senecal & Raymond 2004; Brey 2007).

Antiphospholipid antibodies (APLs) are a heterogenous group of circulating autoantibodies directed against negatively charged phopholipids and protein co-factors. There are at least two distinct groups of APLs; type I occur in patients with infections, type II are frequently found in patients with autoimmune disease. These antibodies are implicated in the pathogenesis of the thrombotic events that characterize the antiphospholipid syndrome (APS). The hallmarks of APS are arterial thrombosis, recurrent fetal loss and thrombocytopenia. A serum co-factor, beta 2 glucoprotein I has been identified as a requirement for in vitro APL antibody binding to phopsholipid and it seems to be the true antigenic target of type II APL (Hanly 1998).

APLs have been reported to be present in 20-55% of SLE patients (Jennekens & Kater 2002). In a review of over 1000 SLE patients, NP manifestations occurred in 38% of patients with lupus anticoagulant compared to 21% of patients without these APL. In addition to prothrombotic effects (below), APLs may exert direct damage to brain tissue. In several studies APLs have been associated with both cerebrovascular disease and cognitive dysfunction in people with SLE and they have also been reported in NPSLE patients with cranial neuropathy, seizures, chorea, headache

and myelopathy (Toubi et al 1995; Hanly 1998; Hanly 1999; Brey 2000; Jennekens & Kater 2002; Denburg et al 2003; Sanna et al 2003; Herranz; Trysberg & Tarkowski 2004; Brey 2007).

Much attention has been directed toward *antineuronal antibodies* with specificity toward antigens on neurons or brain tissue. Positive correlations have been found between antineuronal antibodies and NPSLE. In particular, diffuse NP manifestations; acute confusional state, psychosis and seizures; have been associated with antineuronal antibodies (How et al 1985; van Dam 1991; Kovacs et al 1993). One hypothesis is that antineuronal antibodies bind to neuronal membranes and cause a transient alteration of cell function without cell death or inflammation; this would account for reversibility of symptoms (Moore & Lisak 1995).

Anti-ribosomal P antibodies have been investigated in NPSLE since Bonfa et al 1987 first reported a strong association of them with lupus psychosis. This result was supported by Arnett et al, who found also an association with organic depression. In some patients, psychiatric symptoms seemed to vary in parallel with anti-ribosomal P titers (Bonfa et al 1987; Arnett et al 1996). Not all psychotic patients with SLE have high anti-ribosomal P titers and some studies have also refuted the association between psychiatric symptoms and anti-ribosomal P antibodies, (Moore & Lisak 1995; Gerli et al 2002). Recently a meta-analysis of 1537 patients with SLE found anti-ribosomal P antibodies to be present in one-third of patients with NPSLE as well as in 15-25% of lupus patients without NP manifestations (Kassara et al 2006).

Recently, the potential role of *anti-glutamate receptor antibodies* in cognitive dysfunction and psychiatric disease in patients with SLE has been considered. N-methyl-D-aspartate (NMDA) receptors NR2a and NR2b bind the neurotransmitter glutamate and are present on neurons throughout the forebrain. Hippocampus has the highest density of NMDA receptors. In addition to their putative role in learning and memory, these receptors display altered expression in major psychosis and if engaged by receptor antagonists cause hallucinations and paranoia (Hanly et al 2005). A subset of lupus anti-DNA antibodies has been found to cross-react with the NR2 glutamate receptor in patients with SLE (DeGiorgio et al 2001). In contrast to previous antineuronal antibodies described in SLE, the anti-NR2 glutamate receptor antibodies appear to have a functional consequence leading to neuronal injury in a manner similar to that seen in excitatory amino-acid toxicity (Hanly et al 2005). It has been suggested that they might be involved in damage of the amygdala in human SLE (Arinuma et al 2008) It has been found a correlation between anti-NR2 antibodies with deficits of memory and learning, depression, psychopathic deviate, schizophrenia

and hypomania (Omdal et al 2005). Most studies report that anti-glutamate receptor antibodies are seen in 25% to 30% of patients with SLE but their association with NP manifestations is controversial. A recent study suggests that these antibodies are associated with cognitive dysfunction and hippocampal apoptosis only in the presence of blood-brain barrier disruption (Kowal C et al 2006; Brey 2007). Furthermore, elevated levels of anti-NR2 antibodies in CSF but not in serum have been found to associate with diffuse NPSLE (Arinuma et al 2008).

Table 5. Human autoantibodies associated with NPSLE (Senecal & Raymond 2004, Brey 2007).

Antigenic specificities	Associated clinical manifestations
Neural tissue-spesific autoantibodies	
Anti-neurofilament antibodies	Diffuse CNS presentation
Anti-glial fibrillary acidic protein	Organic/major type NP manifestation
Anti-microtubule-associated protein 2 (MAP-2)	Various NP manifestations
Non-neural tissue-specific autoantibodies	
Anti-dsDNA antibodies cross-reactive with neuronal receptors in the CNS	Progressive cognitive decline (single patient)
Antiphospholipid antibodies	Focal neurologic deficits (strokes, seizures, transverse myelopathy), deterioration in cognitive function
Antilymphocyte antibodies cross-reactive with brain antigens	Encephalopathies, seizures, visuospatial deficits
Antiribosomal P protein antibodies	Controversial association with psychosis and severe depression
Antiganglioside	Controversial association with NPSLE, stronger association with peripheral neuropathy
Anti-glutamate receptor antibodies	Controversial association with cognitive dysfunction and psychiatric disease

7.1.2. Immune complex

Immune complex-mediated tissue injury is a hallmark of SLE, well established in the pathogenesis of renal and cutaneus disease. Immune complexes can activate endothelium, resulting in increased adhesion of leucocytes and enhanced thrombus formation. Much of the interest in immune complexes and neurologic function has developed from the observations that immune complexes appear in CSF, are deposited in the choroid plexus, and can alter the blood-brain barrier when injected to experimental animals. However, evidence for immune complex-triggered inflammation in the CNS is scanty. In brain vessels restrictive tight junctions can prevent the perivascular accumulation of immune complexes. There are immune complex depositions in the choroid plexus also in patients without NP manifestations. Furthermore, neurologic abnormalities are usually not associated with evidence of active elevation of circulating immune complexes (Moore & Lisak 1995, Abbott et al 2006, Senecal & Raymond 2004).

7.1.3. Cytokines

Cytokines, small proteins produced by lymphocytes, macrophages, and other cells, are prominent in the pathogenesis of neurologic disease. They cause biologic effects in cells with receptors for that particular cytokine. Both physiologic and pathologic effects on neurologic function may result (Moore & Lisak 1995). Among other effects, cytokines are capable of inducing production of proteolytic enzymes, metalloproteinases, with ability to destroy brain parenchyma.

Several studies have shown that the level of interleukin-6 (IL-6) in CSF is elevated in patients with NPSLE. Also elevated levels of IL-6 mRNA in the hippocampus and cerebral cortex have been found in autopsies on patients with NPSLE (Efthimiou et al 2009). Il-6 serves as an important growth factor for activated B cells. Increased production of other cytokines such as Il-1, transforming growth factor-B, Il-8, interleukin-10, and interferon-G have also been reported in CSF of patients with NPSLE (Trysberg & Tarkowski 2004).

7.1.4. Activated lymphocytes

Activated lymphocytes may have a pathogenic effort on brain tissue in SLE. Activated immunocompetent cells can penetrate the blood-brain barrier, lodge in the brain, and secrete cytokines, leukotrienes, and prostaglandines. B cells may be the source of intrathecal synthesis of Ig (Moore & Lisak 1995).

7.2. Indirect immune-mediated effects

Immune-mediated indirect neurologic effects typically result from the action of autoantibodies, cytokines, immune complexes, or activated lymphocytes on the vasculature. Neurologic effects result from tissue ischemia. Neurologic abnormalities develop when a critical degree of local disease or a series of sub-clinical events in abnormal blood vessel occur (Moore & Lisak 1995).

7.2.1. Vasculopathy

Vasculopathy refers to structural abnormalities of the blood vessel wall; in NPSLE these changes occur primarily in small but sometimes in medium-sized, vessels (Moore & Lisak 1995). In histopathological studies in NPSLE patients, small-vessel angiopathy, leading to microinfarcts, is the predominant structural abnormality (Johnson & Richardson 1968; Hanly et al 1992; Trysberg & Tarkowski 2004). Changes in the walls of affected vessels include proliferation of intimal cells, increase in fibrous tissue, and mucoid hyperplasia or hyalinization (Jennekens & Kater 2002). Characteristic histopathological features of true vasculitis with a brisk infiltrate of inflammatory cells within the vessel wall is infrequent, it has been documented in only 7% to 15% of NPSLE autopsy cases (Trysberg & Tarkowski 2004). No clinical syndrome of central nervous system has been associated with cerebral vessel spasm (Jennekens & Kater 2002). A microvasculopathy formerly attributed to deposition of immune complexes is now suspected to arise from activation of complement and appears to be the most common microscopic brain finding in SLE. Single photon emission computed tomography (SPECT) and magnetic resonance spectroscopy (MRS) studies suggest that both cerebral atrophy and cognitive dysfunction in SLE patients may be related to chronic diffuse cerebral ischemia. However, these are nonspecific findings, as patients without

overt NPSLE manifestations also show these changes and the brain can be histologically normal in a patient with NP manifestation (Brey 2007).

Numerous epidemiologic studies have showed evidence of accelerated and premature atherosclerosis in patients with SLE. Inflammation plays an important role in the pathogenesis of both SLE and atherosclerotic disease. Traditional Framingham risk factors do not fully account for the elevated and premature risk seen in SLE patients and other factors i.e. inflammatory mediators may also be important in the development of these complications. Premature atherosclerosis is induced in SLE patients by chronic inflammatory processes, dyslipoproteinemia, renal disease and treatment with corticosteroids. However, steroid treatment could actually prevent atherosclerosis as well, because it suppresses inflammation, which is implicated in atherosclerosis. The results of studies about the effect of steroid treatment are conflicting (Esdaile et al 2001; Jennekens & Kater 2002; Rhew et al 2006; de Leeuw et al 2009). .

Endothelial injury is the initial step in atherogenesis. It can occur from a variety of causes e.g. shear stress, viruses, toxins, immune complexes, oxidative stress and complement activation. Injury results in endothelial dysfunction and an inflammatory response which plays a role in all stages of atherogenesis and in the progression of atherosclerosis. This inflammatory response includes the expression of adhesion molecules on the endothelium, secretion of cytokines to recruit further inflammatory cells and induce proliferation of macrophages and smooth muscle cells, differentiation of macrophages and uptake of oxidized LDL by macropahges to become foam cells, with formation of fatty streak and subsequent atheromatous plaque. The final step is release of matrix metalloproteinases (MMPs) and tissue factor by macrophages resulting in plaque rupture and thrombus formation (Rhew et al 2006).

The study of endothelial injury is difficult due to inaccessibility of the endothelium in humans. Endothelial cell activation has been demonstrated in SLE by the presence of increased levels of VCAM-1, thrombomodulin (TM) and von Willebrand factor (vWf), and by increased expression of adhesion molecules in skin biopsy specimens of SLE patients (de Leeuw et al 2009). Circulating endothelial cells (CECs) have recently shown to serve as a new marker for micro-vascular injury. CECs are thought to be mature cells that have detached from the intimal monolayer in response to endothelial injury. An increased number of CECs has been observed in patients with SLE and an association to the disease activity has also been found (Elshal et al 2009).

In addition to being directly responsible for clinical NP syndromes, alternatively vasculopathy may enhance blood-brain barrier permeability, thus facilitating the access of pathogenic antibodies from the circulation into the CNS (Hanly 1998).

7.2.2. Coagulopathies, cardiac emboli and hematologic changes

The relation between APL and CNS involvement in SLE was first reported in 1984 and has later been confirmed; an association of APL with arterial and venous thrombosis in patients with SLE has been shown reliably (Toubi et al 1995). APS is defined by arterial and/or venous thrombosis and recurrent fetal loss in the presence of APLs (Cuadrado et al 2000; Dignat-George et al 2004). The diagnosis of APS is based on clinical and laboratory criteria, defined by strict guidelines. The original clinical and laboratory criteria for the identification of APS patients were published in 1999, in the so-called Sapporo criteria. In 2006 these criteria were revised (Devreese et al 2010).

APLs potentially contribute to stroke by two pathways, interaction with the blood vessel wall and with the coagulation cascade (Moore & Lisak 1995). Several studies have shown that the binding of aPL to endothelial cells induces endothelial activation and/or injury, transforming their antithrombotic surface into a prothrombotic one that could contribute to the acquired hypercoagulable state associated with APS. Activated endothelial cells induce the release of these endothelial-cell derived microparticles. They are pro-coagulant vesicles formed by the endothelial cell membrane after injury or activation. It has been proposed that the generation of microparticles in APS and SLE patients results from an autoimmune process involving APL (Dignat-George et al 2004; Elshal et al 2009).

The European Working Party on SLE followed up a cohort of 1000 patients for a 10-year period and found that thromboses were the most common cause of death and were always associated with APLs (Cervera et al 2003). Other abnormalities leading to a hypercoaguable state in SLE include decreased fibrinolysis, decreased plasminogen activation, and impaired formation of prostacyclin (Moore & Lisak 1995). Cerebral emboli derived from valvular or endocardial vegetations or from carotid plaques may also be the cause of cerebral ischaemia (Jennekens & Kater 2002).

7.3. Non-immune mediated effects

Neurologic complications of SLE may also result from abnormalities not directly related to the primary disease. The major aetiologies in this group are infections, toxins, and metabolic derangements. Infection remains still a leading cause of morbidity and mortality in SLE. The frequency of infections results from the patients` immunosuppression both by medication and by the underlying disease. Corticosteroids and anti-hypertensive medications can produce neurologic and psychiatric symptoms. Metabolic abnormalities affecting the nervous system include uremia and disorders of electrolyte levels (Moore & Lisak 1995).

8. Radiological findings of NPSLE

MRI is more sensitive than computer tomography (CT) for brain lesions associated with NPSLE and, in contemporary practice, is the preferred anatomic imaging modality. MRI relies on two properties of the water molecule that occur after exposure to a depolarizing radio frequency pulse whilst in a constant magnetic field. These properties are T1 relaxation and T2 depolarization. Typically on a T1 weighted image of the brain, the grey matter appears grey, the white matter is white and CSF is dark. T2 weighted imaging is almost the reverse with fluid being bright, such as CSF and inflammatory oedema. There is reversal of the grey and white matter signal intensities, with white matter being darker than grey matter. To enhance the conspicuity of pathological lesions, on T2-weighted images the CSF signal can be dampened to highlight areas of intra and extracellular oedema. This fluid-attenuating inversion recovery sequence (FLAIR) can be used when imaging the brain. Intravenous contrast media MRI, typically gadolinium, can also be used. Using T2-weighted imaging and FLAIR sequence allows visualization of high signal lesions most clearly (Graham et al 2003).

Imaging studies are important in the management of SLE patients with NP involvement for detecting not only changes caused by SLE but also evidence of alternative diagnoses (Sibbitt et al 1989; Huizinga et al 2001; Peterson et al 2005; Castellino et al 2008). Abnormalities on MRI scanning have been found in 19-70% of SLE patients (Hanly et al 2005). No specific MRI abnormalities have been associated with CNS involvement in SLE. Cortical stroke, global atrophy, nonspecific foci of increased signal in both grey and white matter on T2-weighted images, cerebral venous thrombosis, venous infarction, and rarely, intracranial calcifications have been reported on MRI scans of NPSLE patients (Kozora et al 1998; Sibbitt et al 1999; Govoni et al 2004).

Small punctate lesions in white matter are most common MRI findings, they have been reported both in SLE patients with or without NP involvement (Jacobs et al 1988; Mc Cune & Golbus 1988; Sibbitt et al 1989; Cauli et al 1994; Gonzales-Crespo et al 1995; Chinn et al 1997; Hanly 1998, Kozora et al 1998). These lesions are concentrated in subcortical white matter, especially in the frontoparietal regions, but may be seen elsewhere. Periventricular lesions have been particularly associated with APS and can be impossible to differentiate on MRI from multiple sclerosis. White matter hyperintensities increase with age in the general population and are also associated with hypertension. The meaning of these lesions in NPSLE is still doubtful, they have been considered as microinfarcts, demyelination plaques or gliotic lesions. Histopathologic analysis suggests that these lesions are a vascular phenomenon representing small infarcts with loss of nerve fibres and local gliosis (Sibbitt et al 1999; Jennekens & Kater 2002; Peterson et al 2005; Govoni et al 2004; Castellino 2008). The presence of them has been found to associate with duration and severity of the disease, past history of CNS involvement and APL. However, the relevance of these lesions to a specific NPSLE episode is disputable (Jarek et al 1994; Gonzales-Crespo et al 1995; Kozora et al 1998; Sibbitt et al 1999; Peterson et al 2005). They have been suggested to underlie cognitive disorder of SLE patients without any other NP manifestations but contradictory arguments have also been presented (Hanly & Liang 1997; Kozora et al 1998).

Focal neurological symptoms of NPSLE have been found to correlate with structural abnormalities, but MRI is usually normal in NPSLE patients with diffuse symptoms. In one study, only 19% of patients with diffuse presentations had an abnormal MRI scan (Peterson et al 2005). However, when diffuse manifestations are also accompanied by generalized seizures, MRI shows multiple small, high-intensity lesions that often resolve with treatment (West et al 1995; Kozora et al 1998; Hermosillo-Romo & Brey2002; Govoni et al 2004). The differentiation of acute active disease from old chronic lesions is also difficult. The use of gadolinium has been shown to be helpful in delineating active inflammatory lesions (Peterson et al 2005).

A significant degree of brain atrophy has been recognized in patients with SLE, even with SLE patients without NP involvement in comparing with healthy controls. Atrophic changes have been found to be more marked in patients with a history of previous overt NPSLE. The aetiology of cerebral atrophy in SLE patients is unknown. The role of steroid use, disease activity and disease duration in cerebral atrophy is unclear (Chinn et al 1997, Hanly 1998, Kozora et al 1998).

The finding of a normal MRI scan is common in NPSLE and this has prompted the research of other MR-based techniques as well as radionuclide brain scanning to increase sensitivity in the assessment of NPSLE. The applification of several technologies to MR scanning has provided additional opportunities to assess brain metabolism and function. In recent years major advances in neuroimaging techniques has allowed a great improvement in the understanding of SLE pathogenesis (Hanly 2005; Peterson 2005; Castellino 2007).

Magnetic resonance angiography (MRA) permits visualization of cerebral blood flow, although it is probably not optimal for visualization of flow in small calibre vessels that are the ones primarily involved is NPSLE (Castellino et al 2005; Hanly et al 2005).

Magnetic resonance spectroscopy (MRS) is a non-invasive MRI technique that allows the biochemical metabolities in brain tissue to be quantified, thereby providing indirect evidence of cellular changes. The amount of N-acetyl (NA) compounds, which reflect the quantity and integrity of neuronal cells, has been found to be reduced in SLE patients with cognitive dysfunction. An association with elevated IgG APL and cerebral atrophy has also been found. MRS has revealed neurometabolic abnormalities even in white and gray matter that appears normal on conventional MRI. Such abnormalities are believed to reflect neuronal injury or loss and demyelination and have been found during active and quiescent The changes observed are not specific to NPSLE. At this time, MRS is a tool for research purposes only (Peterson et al 2005; Hanly et al 2005, Muscal & Brey 2006).

Diffusion-weighted imaging (DWI) is a MRI application which measures the diffusion of water in the brain. It is highly effective in the detection of hyperacute brain injury, in particular acute ischemia following stroke. So far, few small studies have evaluated DWI in NPSLE. Two of them showed an overall increase in diffusion in NPSLE compared with healthy controls, suggesting inflammation with loss of white-matter integrity (Peterson et al 2005; Castellino et al 2008).

Magnetization transfer imaging (MTI) is a quantitative MRI technique that is sensitive to macroscopic and microscopic brain tissue changes. It measures the magnetization transfer ratio which can be displayed as histograms. MTI is particularly suited to the detection and quantification of diffuse brain damage. Decreased MTR has been correlated with global neurological, psychiatric and cognitive functioning in NPSLE and also with anticardiolipin antibodies (Bosma et al 2002; Hanly et al 2005; Castellino et al 2008).

Positron emission tomography (PET) is a nuclear medicine technique which explores both brain glucose metabolism and cerebral blood flow. Even though PET has high sensitivity, it is abnormal in 100% patients with active NPSLE, due to low specificity, limited availability, excessive cost and elevated dose radiations it is rarely applied in daily clinical practise. *Single photon emission computed tomography* (SPECT) is more easily available nuclear medicine technique which provides semi quantitative analysis of regional cerebral blood flow and metabolism. It is exquisitely sensitive and in studies of SLE patients has identified both diffuse and focal deficits which may be fixed or reversible (Hanly et al 2005; Castellino et al 2008).

9. Diagnosis and follow up of NPSLE

There is no single diagnostic test that is sensitive and specific for SLE-related neuropsychiatric manifestations. The assessment of individual patients is based on clinical neurologic and rheumatologic evaluation, immunoserologic testing, brain imaging, and psychiatric and neuropsychological assessment. The spectrum of diagnostic tests available is listed in table 6. An important consideration in the diagnostic approach to a patient with possible NP manifestation is whether the syndrome is convincingly attributed to SLE, a complication of the disease or its therapy, or whether it reflects a coincidental disease. Infection is a major cause of central nervous system syndromes in hospitalized SLE patients so it always has to be suspected. Examination of CSF should be considered primarily to exclude infection. Measurement of CSF autoantibodies, cytokines and biomarkers of neurologic damage is still a subject of research. APL are the circulating antibodies most likely to provide the greatest diagnostic yield. Neuroimaging should include a modality to assess brain structure and another to assess brain function. Currently the most accessible and available techniques are MRI and SPECT (Hanly et al 2005; Brey 2007; Castellino et al 2007).

Table 6. Investigations in the assessment of SLE patients for NP disease (Hanly & Harrison 2005).

Type of investigation	
CSF	Exclude infection
	Autoantibodies
	Cytokines
	Biomarkers
Autoantibodies	Antiphospholipid
	Antiribosomal
	Antineuronal
Neuroimaging	Brain structure (CT, MRI)
	Brain function (PET, SPECT, MRI, MRA, MRS, MTI, DWI, FMRI)
Neuropsychological assessment	

CSF, cerebrospinal fluid; CT, computerized tomography; DWI, diffusion weighted imaging; fMRI, functional MRI; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MTI, magnetization transverse imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography

10. Treatment of NPSLE

The management of patients with SLE includes symptomatic, immunosuppressive and anticoagulant therapies, but evidence for the efficacy of the treatment modalities commonly used is largely limited to uncontrolled trials and anecdotal experience. The key to treatment is to first establish the correct diagnosis by carefully considering all possible aetiologies, both SLE-related and those which are not. The choice depends on the most probable underlying pathogenic

mechanism and the severity of the presenting NP syndrome. Potential aggravating factors such as hypertension, infection, toxic effects of therapy and metabolic abnormalities have to be identified and treated. Immunosuppressive therapy may be associated with several opportunistic infections of the brain and differentiation between primary CNS involvement and CNS infection may be extremely difficult. Patients with mild manifestations may need symptomatic treatment only, for example, anticonvulsants, antidepressants, anxiolytics and antipsychotic medications, whereas more severe acute nonthrombotic CNS manifestations may require intravenous pulse cyclophospamide therapy. Immunosuppressive therapy with hydroxychloroquine, corticosteroids, azathioprine, methotrexate and cyklophosphamide are used to varying degrees (Table 7.). Plasmapheresis may also be added in patients with more severe illness refractory to conventional treatment (Navarrette & Brey 2000; Hermosillo-Romo & Brey 2002; Sanna et al 2003; Hanly et al 2005).

Hydroxychloroquine (HCQ) is commonly used to treat mild disease. Recently it has been postulated that HCQ should be given to most patients with SLE during the whole course of the disease because high levels of evidence were found that antimalarials prevent lupus flares and increase long-term survival of patients with SLE. The precise mechanism of action is not well understood, but it is suspected that antimalarials may function as immunomodulators in systemic inflammatory disorders (Navarrete & Brey 2000). They might operate by inhibiting the activation of intracellular TLRs. It has been suggested that they can slightly increase the pH within endosome in antigen-presenting cells or B cells interfering with autoantigen presentation. The pH elevation reduces the affinity binding between immune complex containing nucleic acids and intracellular TLRs, decreasing the expression of type I interferon genes which represent an early stage in the pathogenesis of SLE (Doria et al 2008). HCQ has relatively minor side effects and it also reduces the incidence of thrombotic events and lessens the hyperlipidemic effects of prednisone. It can be used during pregnancy. Hydroxychloroquine is also a potential additional treatment for APS (Navarrete & Brey 2000; Ruiz-Irastorza et al 2010).

Although the approach to corticosteroid therapy remains largely empirical, corticosteroids continue to represent the first line of treatments for SLE with suspected diffuse CNS involvement. Tablets of prednisone are given orally and the dose is individualized. High-dose glucocorticoids are indicated for acute severe CNS manifestations. 1 g of intravenous methylprednisolone is given daily or every other day for a total of three to six doses. A randomized controlled clinical trial comparing long-term use of cyclophosphamide and methylprednisolone reported a better overall therapeutic control of SLE-related neurologic manifestations with monthly intravenous cyclophosphamide. The use of

intravenous cyclophospamide is the recommended current practise in cases of acute severe CNS disease, in those refractory to corticosteroids or when a steroid-sparing effect is desired. It is administered in a dose of 750 to 3000 mg/m2; no more than 1000 mg is given as a single dose (Navarrette & Brey 2000; Hermosillo-Romo & Brey 2002; Sanna et al 2003; Hanly et al 2005; Brey 2007; Muscal & Brey 2010).

Plasmapheresis is useful to remove free antibodies, complement components and circulating immune complexes. The efficacy of plasmapheresis is anecdotal and it seems that patients who respond to this treatment are those with more severe illness, refractory to corticosteroids and cyclophosphamide therapy, and with the highest levels of circulating immune complexes; generally it is considered for the treatment of NPSLE only when all other possibilities have been tried and have been found to be ineffective (Navarrette & Brey 2000; Sanna et al 2003).

Intravenous immunoglobulin (IVIg) has proved to be useful in the treatment of autoimmune and inflammatory neurological diseases, but there are only few reports of the use of IVIg in NPSLE. However, beneficial effects of high-dose IVIg have been shown in a patient with SLE and acute severe CNS disease, including psychosis (Sanna et al 2003). The mechanism of action of IVIg is unclear, but possibilities include an anti-idiotypic antibody effect, Fc receptor blockade, suppressor cell enhancement, and inhibition of lymphocyte proliferation (Navarrette & Brey 2000).

In general, the current treatment for SLE, not only neuropsychiatric one, is nonspecific and is associated with serious adverse effects by causing generalized immunosuppression. In addition, a significant number of lupus patients show only partial or no response to the current therapies. Therefore, more specific treatments for SLE are sought. Especially in interest are therapies that target B-cells, including B-cell depletion using monoclonal antibodies that bind B-cell surface antigens. Rituximab and epratuzumap have shown good therapeutic results (Tieng et al 2008). In ten patients with refractory NPSLE, despite intensive treatment, treatment with rituximab resulted in rapid improvement of CNS-related manifestations, particularly acute confusional state. It also improved cognitive dysfunction, psychosis and seizures (Tokunaga et al 2007). Other B-cell targeted therapies are focused on specific B-cell functions involving inactivation of autoreactive B-cells via tolerance induction, blockade of costimulatory signals, or blockade of cytokines that stimulate B-cells. Many different biological agents have been used in recent and ongoing studies, but up to now breakthroughs emerging from randomized Phase III trials have been rare (Tieng et al 2008; Haubiz 2010).

Anticoagulation is strongly indicated for focal disease when APLs are implicated and such therapy will usually be lifelong. The use of antiplatelet or anticoagulant therapy in SLE patients with APLs for the treatment of cognitive dysfunction without evidence of thromboembolic phenomena has never been studied and remains controversial. In APS, possible future therapies are statins, rituximab, and new anticoagulant drugs (Ruiz-Irastorza et al 2010). So far there is no data to support or refute the use of pharmacologic agents developed for the treatment of cognitive dysfunction associated with Alzheimer´s disease and attention deficit disorder, in the treatment of SLE-associated cognitive dysfunction (Hanly et al 2005).

Nonpharmacologic approaches are also important in SLE patients with psychiatric disorders and cognitive dysfunction. In a study, SLE patients receiving psychological group intervention have showed a significant and sustained improvement in several symptoms, such as depression, anxiety, and overall mental burden. Lupus patients with verified cognitive dysfunction can be referred for cognitive rehabilitation to a neuropsychologist (Hanly et al 2005; Muscal & Brey 2010).

Table 7. Immune-modulating therapy for neuropsychiatric systemic lupus erythematosus (Navarrette & Brey 2000)

Therapeutic agent	Indications
High-dose glucocorticoids	Seizures in the presence of active SLE Cerebral vasculopathy* Any CNS manifestation in the presence of active SLE
Intravenous pulsed cyclophosphamide	Cerebral vasculopathy* Nonthrombotic focal neurologic deficits in SLE* Transverse myelitis*
Hydroxychloroquine	Long-term control of active SLE Antiplatelet effect Cholesterol-lowering effect
Intravenous immunoglobulin	Any CNS manifestation unresponsive to glucocorticoid therapy, cytotoxic therapy, or the combination
Plasmapheresis	Any CNS manifestation unresponsive to glucocorticoid therapy, cytotoxic therapy, the combination, or intravenous immunoglobulin

*May require the combination of both high-dose glucocorticoid and intravenous cyclophosphamide

CNS, central nervous system; SLE, systemic lupus erythematosus

AIMS OF THE STUDY

The purpose of this cross-sectional, population-based study was to

1. describe the prevalence of NP syndromes in a Finnish population of SLE patients and classify the syndromes according to the ACR nomenclature and case definitions.
2. assess the validity of the ACR nomenclature and case definitions for NPSLE
3. investigate whether there is any association between the volumes of MRI lesions and NP manifestations in SLE
4. evaluate and test the hypothesis whether serum MMP-9 levels are associated with NP manifestations or cerebral MRI abnormalities in SLE patients

PATIENTS AND METHODS

1. Patients and study design

The study base was Pirkanmaa Health Care District located in Southern Finland with a population of 440 000. The majority of the new SLE patients in the area are seen at Tampere University Hospital. Patients with SLE were identified by using the computerized data-base of Tampere University Hospital, the three District Hospitals and the local outpatient clinic. Medical records of both in- and out patients coded for the diagnosis of SLE between January 1980 and December 1997 were examined to select patients who fulfilled four or more of the 1982 revised ACR criteria for the disease, were aged 16-65 years and of native Finnish origin, and resident in the study area. Patients with another connective tissue disease were excluded.

A total of 110 SLE patients were identified. Of these, 15 patients had died and 37 did not meet the inclusion criteria. The remaining 58 patients were contacted by mail and 46 of them (79%) agreed to participate in the study. The control group consisted of 46 individuals randomly identified from the Finnish Population Register, with matching on age, sex, level of education and municipality of residence. Similar eligibility criteria were applied as for the cases.

All participants gave their written informed consent. The study protocol was approved by the local Ethics Committee.

2. Methods

2.1. Clinical examination

A complete medical history was obtained from all patients and a clinical neurological examination was performed by the same neurologist (H.A.) between November 1998 and May 1999. Furthermore, patient files were thoroughly perused in order to find evidence of past neurological disorders. The diagnosis of various NP syndromes was based upon the clinical impression following history, clinical neurologic examination and review of the medical records and

performance in neuropsychological testing. All past and present NP syndromes were listed and classified according to the standardized ACR nomenclature and case definitions (ACR 1999) (I and II) or according to the modified ACR nomenclature and case definitions (II) (III and IV) (Tables 3 and 12). If one of the NP syndromes was identified, a patient was considered to have NPSLE. Individual disease activity was quantified by using the ECLAM (Vitali et al 1992). Accumulated NP abnormality was assessed by using the SLICC/ACR damage index (Gladman & Urowitz 1999). The NP manifestations of the damage index scored were cognitive impairment, major psychosis, seizures requiring therapy for 6 months, cerebral vascular accident, cranial or peripheral neuropathy (excluding optic) and transverse myelitis. Current and previous use of steroid and other immunosuppressive medication was recorded. A cumulative lifetime dose of glucocorticoids (expressed as grams of prednisolone) was determined from the patients' records.

2.2. Serological and immunological methods

Blood samples for laboratory studies were obtained from all patients and controls at the time of the study. Laboratory tests included a complete blood count, erythrocyte sedimentation rate (ESR), serum complement components (C3, C4 and CH50), anti-dsDNA, ANA and APL. APL were tested measuring IgG type anticardiolipin antibodies (ACL) by ELISA (commercial kit). Results were expressed in GPL units. ACL were reported as either medium positive (15-80 GPL) or high positive (>80 GPL). In cases where ACL were positive, also β2-glycoprotein antibodies (β2GPAbG) were measured by ELISA and reported as negative (<20 SGU) or positive ($\geq$20 SGU). In SLE patients, serum creatinine and urinalysis were also measured to determine the disease activity index.

Quantitation of immunoreactive matrix metalloproteinase-9 (MMP-9) was carried out by enzyme-linked immunosorbent assay (ELISA) (Diabor Ltd, Finland). This method is described in study III. The monoclonal antibody GE-213 recognizes both pro and activated forms of human MMP-9 and the complex of MMP-9 with its inhibitor TIMP-1 (Soini et al 1994, Nikkari et al 1996). In two patients and three controls, determination of MMP-9 level was not successful.

2.3. Neurophysiological methods

Neurophysiological tests included electroneuromyography (ENMG), which was performed only on 12 patients with clinical signs or symptoms suggesting polyneuropathy.

2.4. Neuropsychological methods

All patients and controls were submitted to a battery of standardized neuropsychological tests in order to detect possible impairment in one or more of the subsequent cognitive domains: simple attention, complex attention, memory, visuo-spatial processing, language, reasoning/problem solving, psychomotor speed, and executive functions. The test battery included is described in study I. It took an average of 3-4 hours to complete the assessment.

The individual test results were converted into standard scores, which were compared with the available normative data (Delis 1987; Wechsler 1992; Lezak 1995; Heaton et al 1993). Regarding any of the eight cognitive domains, subjects with a total score of two or more standard deviations (SD) below the normative value were considered to be impaired. Premorbid level of functioning was estimated by using the two best scores from WAIS-R, excluding Digit Symbol Substitution Test and Digit Span. Education and occupation of the subject were taken into consideration in assessment of individual test performance. The same method was used to determine the highest level of functioning in controls. Cognitive dysfunction was classified as mild if there were deficits in less than three dimensions, as moderate if there were deficits in three or four dimensions, and as severe if there were deficits in at least five dimensions.

Assessment of depression was based on clinical interview and the Beck Depression Inventory (BDI) (Beck et al 1974). On BDI, scores from 10 to 17 were considered to be mild, scores from 18 to 24 to be moderate and scores over 24 to indicate severe depression. However, the final grading of depression was based on a clinical interview by the psychologist. Anxiety was evaluated by the psychologist on clinical interview.

2.5. Neuroradiological methods

Cerebral MRI was performed on 43 SLE patients and 43 healthy controls. The Signa Easy Vision 1.5T MRI imaging system (General Electric Medical Systems, Milwaukee, WS, USA) was used for all examinations. All MRI scans were read in a blinded manner by an experienced neuroradiologist (PD) who did not have access to any demographic or clinical data. The MRI study was carried out within six months of the clinical evaluation (the mean time was 11.1±11.6 weeks for the SLE patients and 17.1±7.6 weeks for the controls). The MRI protocol included sagittal T1-weighted, axial T1-weighted, axial T2-weighted and coronal fluid-attenuated inversion recovery (FLAIR) sequences. The imaging protocol also included axial 3-dimensional (3-D) T2 fast spin-echo and gadolinium diethylenetriamine pentaacetic acid-enhanced 3-D T1 spoiled gradient images for segmentation and volumetric analysis. Segmentation and volumetric analysis were performed using the segmentation software called Anatomatic, operating in PC/Windows95™ environment (Heinonen et al 1998; Heinonen et al 1998; Dastidar et al 1999). Segmentation and volumetric measurements of hypointense lesions in T1-weighted images and hyperintense lesions on T2-weighted images were performed separately.

The criteria for SLE-related imaging abnormalities were as follows: gliotic infarcts and gliotic plaques seen as hypointense lesions on T1-weighted images and microinfarcts, ischemic lesions, demyelinating plaques as well as small punctate white matter lesions localized to the periventricular and subcortical areas on T2-weighted images. Small age-related lesions were excluded from analysis. The criteria for age-related changes were as follows: small periventricular T2-weighted high signal intensity changes in the area of frontal and occipital horns; few scattered well-defined small-size (<3mm) T2-weighted high signal intensity changes in the area of centrum semiovale not visible on T1-weighted images, and widened Virchow-Robin spaces seen as low signal intensity areas on FLAIR images. Measurements were expressed as volume/cm^3.

The marker for cerebral atrophy was relative intracranial cerebrospinal fluid (CSF) space volume. Volumetric measurement of total CSF spaces was done by assessing the total volume of the ventricular and peripheral CSF spaces, expressed as volume/cm^3. Total intracranial volume was measured by calculating together the volume of all the segmented grey and white matter and intracranial CSF spaces. Relative intracranial CSF space volume was determined by dividing the total intracranial CSF space volume by the total brain volume.

Inter- and intra-observer variability was studied to evaluate the accuracy of the volumetric measurement of the lesions; the methods and results are described in study IV.

2.6. Statistical analysis

The prevalence of each condition included in the ACR criteria was calculated for SLE cases and controls. The odds ratio (OR) was calculated as the ratio of discordant pairs with a positive case to pairs with a positive control. The data were analyzed with conditional logistic regression methods, using presence or absence of SLE as the outcome measure and various diagnostic criteria as explanatory variables.

Pearson Exact Chi-Square test for cross-tabulated data, two-sample Student´s T-test and Mann-Whitney U-test were used to evaluate the association between the occurrence of any NP manifestation and current or prior steroid use. The limit for significance was set equal to 0.05.

Differences in MRI parametres between the study groups were determined using the Mann-Whitney U Test. The correlations between MRI parametres and laboratory values and cumulative dose of glucocorticoids were analyzed using Spearman's rank order correlation. The criterion for statistical significance was p-value less than 0.05.

Differences in levels of serum MMP-9 between study groups were tested by using the Mann-Whitney U Test or nonparametric ANOVA. The correlation between MRI parametres and serum MMP-9 levels was analyzed using Spearman's rank order correlation. Differences in levels of serum MMP-9 between ECLAM and SLICC/ACR groups were tested by using analysis of variance (ANOVA). The criterion for statistical significance was p-value less than 0.05.

RESULTS

1. Basic characteristics of SLE patients and controls

The study group consisted of 39 female and 7 male SLE patients, with a mean age of 45±13 years (range 20-64), and a similar number of matched controls (Table 8). The mean disease duration since diagnosis of SLE was 14±8 years (range 2-37) and the mean number of ACR SLE criteria fulfilled was 5.5±1.2 (range 4-9) (Table 9). The mean ECLAM score was 1.7 (range 0-4) indicating a very mild disease activity. Patients had completed 13±2.7 (range 8-18) and controls 13± 3.4 (range 7-20) years of education. At the time of the study, 25 patients (54%) were using glucocorticoids, seven (15%) were on antimalarials, five (11%) on azathioprine, two (4%) on methotrexate and one (2%) on cyclosporin. Nineteen patients (41%) were without specific medication. For those who had taken glucocorticoids, the median cumulative lifetime dose of prednisolone was 26 grams (range 1-89). A total of four patients (9%) had never used glucocorticoids.

Table 8. Baseline characteristics of 46 SLE patients and 46 controls.

	SLE patients Mean (SD)	Controls Mean (SD)
Age, years	45 (12.6)	45 (12.7)
Sex (M/F)	7/39	7/39
Disease duration,yrs	14.2 (8.0)	-
Education years, mean	13 (2.7)	13 (3.4)

*Statistics:Mann-Whitney U Test

Table 9. The diagnostic ACR criteria in 46 SLE patients.

Criterion	n	(%)
Malar rash	26	(57)
Discoid rash	4	(9)
Photosensitivity	28	(61)
Oral ulcers	8	(17)
Arthritis	31	(67)
Serositis	12	(26)
Renal disorder	18	(39)
Neurologic disorder	4	(9)
Hematologic disorder	33	(72)
Immunologic disorder	43	(93)
Antinuclear antibody	46	(100)

2. NP syndromes

According to the ACR nomenclature and case definitions, at least one NP syndrome was identified in 42 of 46 patients (91%). Five patients (11%) had one, 12 patients (26%) had two, 15 patients (33%) had three, four patients (9%) had four, four patients had five (9%) and two patients (4%) had six NP syndromes, whereas only in four patients was no evidence of NP syndromes detected. Np syndromes detected in patients and controls are shown in Table 10.

The most frequent single manifestation was cognitive dysfunction, detected in 37 patients (80%). Memory dysfunction was the most affected domain registered in 20 patients (43%), followed by deficits in simple attention, visuospatial processing and psychomotor speed, each in 12 patients (26%). Only 14 out of 37 patients (38%) with cognitive dysfunction by testing complained of cognitive problems, mostly defined as impairment of memory, concentration and word finding. Similar complaints were also done by two patients showing no cognitive deficits by testing.

Headache was diagnosed in 25 patients (54%). This syndrome consisted of migraine without aura in six (24 %), migraine with aura in 12 (48%) and tension headache in seven patients (28%). Cluster headache and pseudotumor cerebri were not detected.

Depression was detected in 15 patients by BDI and in five additional patients by psychological interview, totalling mood disorder in 20 patients (43%). It consisted of a major depressive-like episode in 18 and a mood disorder with mixed features in two patients. The severity was mild in 16 and moderate/severe in four cases**.**

Clinical findings possibly related to polyneuropathy were detected in 13 patients (sensory defects in four and sensorimotor in nine patients). However, only four patients had subjective symptoms (gait disorder, numbness). An ENMG was performed for 12 patients (one patient died before the examination) and the electrophysiological findings were consistent with polyneuropathy in only three of them.

Seven patients (15%) had a history of cerebrovascular disease. Five patients had had a stroke syndrome, one of them twice. TIA was occurred in two patients, and in one patient, a chronic multifocal disease was diagnosed. No intracerebral hemorrhages were recorded. Mean time since the diagnosis of SLE to the occurrence of the first stroke or TIA was 10.7 years (range 1-18). In four patients cerebrovascular disease was concomitant with systemic disease activity. APL were moderately positive in four patients with cerebrovascular disease.

Epileptic seizures were reported in four patients (9%). In three of them, the diagnosis of epilepsy had been made and they were all on anticonvulsants. The first seizure occurred in all of them after the diagnosis of SLE. One patient had experienced only one tonic clonic seizure, which had occurred during a disease flare. All three patients with epilepsy had a moderately positive level of APL.

An acute confusional state had occurred in three patients (7%). In two of them, symptoms had manifested simultaneously with a lupus flare. In one patient, mild disturbance of consciousness had lasted for a week, in the other, moderate symptoms had abated within a month. The third patient had experienced two severe episodes of confusional state within a year. At the first time, her symptoms improved a little within two weeks, leaving, however, a significant memory deficit as a residual symptom. After the second episode, further cognitive decline was noticed.

Three patients (7%) had a history of cranial neuropathy, which was in all cases an optic neuritis. In one patient, an optic neuritis had occurred 16 years before and in another 29 years before the diagnosis of SLE. In the third patient, optic neuritis manifested 5 years after SLE diagnosis.

One patient (2%) was diagnosed to suffer from myasthenia gravis. The duration of the disease was 26 years and its severity according to Osserman classification was IIA (mild generalized myasthenia with no crises and good response to drugs). The presenting symptoms of myasthenia gravis included diplopia, bilateral ptosis, and physical activity related weakness of lower extremities and they appeared about ten years after the diagnosis of SLE

One patient (2%) had a demyelinating syndrome. The neurological symptoms appeared with subacute onset 18 years after the diagnosis of SLE. In cerebrospinal fluid examination, IgG index was elevated and eight oligoclonal bands were present indicating intrathecal synthesis. Increased signal in periventricular white matter and at the level of corona radiata on T2-weighted MRI scans was observed. Both aCL (151 GPL) and β2GPAbG (333 SGU) were in high positive range.

One patient (2%) had had aseptic meningitis three years prior to the diagnosis of SLE.

One patient (2%) had an episode of involuntary, choreoathetotic movements occurring in all limbs. The severity of the symptom was moderate. This episode occurred nine years after the diagnosis of SLE and abated within a year without recurrence. It was associated with a disease flare.

In addition, the following neurological symptoms, not included in the ACR nomenclature, were identified in SLE patients. Nine patients (20%) suffered from fatigue, three (7%) had essential tremor, and two had had bacterial meningitis. Writer's cramp, myopathy, sleep apnea and carpal tunnel syndrome occurred each in one patient. Urinary problems occurred in five patients (11%). Four of them had slight/moderate urge incontinency and one patient slight difficulty in initiation. The diagnosis of fatigue and urinary problems was based entirely on subjective complaints of the patients.

A total of six NP syndromes defined by ACR were not identified in this population. These include inflammatory demyelinating polyradiculoneuropathy, autonomic disorder, mononeuropathy, myelopathy, plexopathy and psychosis.

There was a statistically significant association between a history of headache and current steroid use ($\chi 2$= 4.114, p=0.043). Compared with other SLE patients, those with a history of epileptic seizures (65.0gm versus 23.0gm; t= 3.319, p= 0.002) or cerebrovascular disease (45.4gm versus 22.7gm; t= 2.288, p= 0.028) had a higher cumulative lifetime dose of steroids. No other statistically significant associations between the occurrence of NP manifestation and steroid use were noticed.

Table 10. Neuropsychiatric syndromes in SLE-patients and controls n (%).

Neuropsychiatric syndrome	Patient n (%)	Control n (%)	OR(95%CI)
Cognitive dysfunction	37 (80)	13 (28)	9.0 (2.7-29.7)
Mild	26	11	
Moderate	7	2	
Severe	4	0	
Headache	25 (54)	11 (24)	3.0 (1.3-7.1)
Migraine without aura	6	4	
Migraine with aura	12	5	
Tension headache	7	2	
Mood disorders	20 (44)	4 (9)	9.0(2.1-38.8)
Major depressive like episode	18	4	
Mood disorder with mixed features	2	0	
Polyneuropathy	13 (28)	5 (11)	3.7 (1.0-13.1)
ENMG confirmation	3	0	
Cerebrovascular disease *	7 (15)	0	∞
Stroke syndrome	5		
Transient ischemic attack	2		
Chronic multifocal disease	1		
Anxiety disorder	6 (13)	3 (7)	2.0 (0.5-8.0)

Table 10. continues

Neuropsychiatric syndrome	Patient n (%)	Control	OR (95 %CI) n (%)
Seizures	4 (9)	1 (2)	4.0 (0.5-35.8)
Acute confusional state	3 (7)	0	∞
Neuropathy, cranial[ψ]	3 (7)	0	∞
Aseptic meningitis	1 (2)	0	∞
Demyelinating syndrome	1	0	∞
Movement disorder	1	0	∞
Myasthenia gravis	1	0	∞

[*]one patient had both a stroke and a TIA

[ψ]optic neuritis in all cases

3. Validity of the ACR criteria for NP syndromes

All syndromes included in the proposed ACR criteria for NPSLE were more frequent among SLE patients than controls (Table 10). However, most syndromes were also found among controls, which resulted in low specificity. At least one NP syndrome was identified in 42 SLE patients (91%) and 25 controls (54%). This corresponds to an odds ratio (OR) of 9.5, 95% CI 2.21-40.8, and yields a specificity of 0.46 (21/46) and a detection rate of 91% (42/46) among SLE patients (Table 11).

To improve the criteria, revised criteria based on objective findings only were constructed (Table 12). Anxiety and headache were entirely excluded, as well as mild depression, mild cognitive dysfunction (with deficits in less than three dimensions) and polyneuropathy unconfirmed by ENMG. With these modifications, the proportion of controls fulfilling at least one of the criteria

was substantially lower (7% versus 54%). Also the proportion of SLE patients with at least one objective criterion was half of that for the proposed ACR criteria (46% versus 91%). With a cut-point of one, the OR for the revised criteria was 7.00 (95% CI 2.09-23.47), with a specificity of 0.93 (43/46) and detection rate among SLE cases 46% (21/46).

No major differences in the validity of the revised criteria were observed, when compared by age, sex or disease duration. The revised criteria showed a slightly higher correlation with neuropsychiatric SLICC damage index than the proposed ACR criteria (r=0.79 versus 0.58, respectively). Neither ACR nor the revised criteria were correlated with current disease activity, as measured with ECLAM (r=0.08 for both).

Table 11. Number of the ACR criteria and the revised criteria for neuropsychiatric SLE among patient and control groups.

ACR criteria	Patients	Controls	OR (95%CI)	Specificity
>0	42	25	9.5 (2.2-40.8)	0.46
>1	37	10	7.8 (2.7-22.0)	0.78
>2	25	2	24.0 (3.3-177.4)	0.96
>3	10	-	∞	1.00
Revised criteria				
>0	21	3	7.0 (2.1-23.5)	0.93
>1	9	0	∞	1.00
>2	6	0	∞	1.00
>3	2	0	∞	1.00

Table 12.The modified criteria for neuropsychiatric SLE.

Central nervous system	Peripheral nervous system
Aseptic meningitis	Acute inflammatory demyelinating polyradiculo-neuropathy
Cerebrovascular disease	Autonomic disorder
Demyelinating syndrome	Mononeuropathy, single/multiplex
Movement disorder (chorea)	Myasthenia gravis
Myelopathy	Neuropathy, cranial
Seizure disorders	Plexopathy
Acute confusional state	Polyneuropathy (with ENMG confirmation)
Cognitive dysfunction (moderate or severe)	
Severe depression	
Psychosis	

4. Neuroradiological findings

4.1. The values of MRI parametres

The analysis based on Anatomatic segmentation software showed that both the mean volume of T1-weighted lesions (representing primarily gliotic infarcts) and the mean volume of T2-weighted lesions was higher in SLE patients than in controls ($p=0.019$ and $p<0.0001$, respectively). In the assessment of brain atrophy it was found that the mean relative intracranial CSF space volume was significantly higher in SLE patients compared with healthy controls ($p<0.001$). The values of MRI parametres in SLE patients and controls are described in study IV, Table 2.

4.2. Association of MRI findings with NP manifestations

The cerebral MRI parametres were determined separately in 19 patients with NPSLE and 24 patients without (non-NPSLE). All the measured parametres were statistically significantly higher in patients with NPSLE than in patients with non-NPSLE (Table 2. in study IV).

The relationship between MRI parametres and all but two NP manifestations was investigated in SLE patients (myasthenia gravis and polyneuropathy were excluded) (Table 13). SLE patients with cognitive impairment had more significant cerebral atrophy ($p=0.008$) and significantly larger volumes of T2-weighted lesions ($p<0.001$) and a trend for larger volumes of T1-weighted lesions ($p=0.077$) than patients who were tested as cognitively normal. The SLE patients with a history of cerebrovascular disease had increased volumes of T1-weighted lesions ($p=0.004$) and T2-weighted lesions ($p<0.001$), but also brain atrophy ($p=0.001$). SLE patients with epileptic seizures had more significant cerebral atrophy than patients without ($p<0.001$) and also T1-weighted lesions ($p=0.049$). Of the other neuropsychiatric manifestations only a single patient with a movement disorder had a statistically significantly higher volume of T1-weighted lesions than the patients without ($p=0.047$).

Neuropsychiatric damage index SLICC correlated significantly with all the measured MRI parametres in SLE patients (Table 14).

Table 13. MRI volumes in the classified neuropsychiatric manifestations in 43 SLE patients.

Neuropsychiatric manifestation		Relative intracranial CSF volume	
	n	mean	p-level*
Cognitive dysfunction			
Yes	10	0.25	**0.008**
No	33	0.17	
Cerebrovascular disease			
Yes	6	0.28	**0.001**
No	37	1.18	
Seizure disorders			
Yes	4	0.33	<**0.001**
No	39	0.18	
Severe depression			
Yes	4	0.23	0.86
No	39	0.19	
Neuropathy, cranial			
Yes	3	0.21	0.40
No	40	0.19	
Acute confusional state			
Yes	2	0.26	0.20
No	41	0.19	
Movement disorder			
Yes	1	0.32	0.14
No	42	0.19	
Aseptic meningitis			
Yes	1	0.28	0.28
No	42	0.19	
Demyelinating syndrome			
Yes	1	0.15	0.70
No	42	0.19	

Abbreviations: MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; CSF, cerebrospinal fluid.
*Statistical significance was based on Mann-Whitney U-test

Table 13. continues

Neuropsychiatric manifestation	n	T1-weighted lesions mean	T1-weighted lesions p-level*	T2-weighted lesions mean	T2-weighted lesions p-level
Cognitive dysfunction					
Yes	10	0.98	0.077	2.01	<**0.001**
No	33	0.32		1.08	
Cerebrovascular disease					
Yes	6	1.97	**0.004**	2.29	<**0.001**
No	37	0.23		1.13	
Seizure disorders					
Yes	4	2.19	**0.049**	1.95	0.167
No	39	0.30		1.23	
Severe depression					
Yes	4	0.14	0.762	1.59	0.319
No	39	0.50		1.27	
Neuropathy, cranial					
Yes	3	0.19	0.911	1.51	0.451
No	40	0.49		1.28	
Acute confusional state					
Yes	2	3.76	0.434	2.09	0.124
No	41	0.31		1.26	
Movement disorder					
Yes	1	7.51	**0.047**	2.46	0.186
No	42	0.30		1.27	
Aseptic meningitis					
Yes	1	0.00	0.698	2.12	0.233
No	42	0.48		1.28	
Demyelinating syndrome					
Yes	1	0.36	0.465	1.67	0.791
No	42	0.47		1.29	

4.3. Association of MRI findings with other clinical features

Correlations between the MRI parametres and clinical features of patients (Table 14) and controls were measured. A significant correlation was detected between the duration of SLE and cerebral atrophy (r=0.39, p=0.010), but not between the disease duration and the volumes of T1-weighted or T2-weighted lesions. The volumes of T2-weighted lesions correlated positively with age both in the SLE patient (r=0.33, p=0.03) and in the control groups (r=0.42, p=0.005). A significant correlation between age and cerebral atrophy was also observed in the controls (r=0.53, p=0.020) but not in SLE patients. No significant correlation between MRI parametres and the activity index ECLAM was found. Similarly, no association was detected between MRI parametres and the use of medication, but a clear positive correlation between the cumulative dose of glucocorticoid and parameter of cerebral atrophy was found (p=0.023).

In SLE patients, no association was detected between the MRI parametres and laboratory findings. Instead, in the control group, a positive significant correlation was found between the volumes of T2-weighted lesions and all the measured complement levels (r=0.31, p=0.04 for complement C3; r=0.49, p=0.001 for complement C4; r=0.36, p=0.02 for CH50) and between cerebral atrophy and complement C4 (r=0.44, p=0.003).

Table 14. Correlations of MRI volumes with various clinical features in 43 SLE patients.

MRI parameter	Age	Duration of SLE	Cumulative dose of steroid	ECLAM score	NP-SLICC score
Relative intracranial CSF space volume	0.22	0.39*	0.38*	0.040	0.69**
T1-weighted volume	0.17	0.11	0.40*	-0.23	0.52**
T2-weighted volume	0.031*	0.19	0.22	-0.024	0.69**

Abbreviations: MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; ECLAM , European Consensus Lupus Activity Measurement; NP-SLICC, Neuropsychiatric Systemic Lupus International Collaborating Clinics

Statistical values were determined by Spearman's rank order correlation test: * $p<0.05$, ** $p<0.01$

5. Serological and immunological findings

The mean level of MMP-9 in SLE patients was 56.7±39.4 μg/l (mean±SD) and in controls 58.8±23.9 μg/l. The difference did not reach statistical significance (p=0.13). Other laboratory values in patients and controls are presented in Table 15.

Table 15. Laboratory parametres of SLE patients and controls.

	SLE patients Mean (SD)	Controls Mean (SD)	p*
Serum MMP-9 (μg/L)	56.7 (39.4)	58.8 (23.8)	0.13
B-Leucocytes (10^9L^{-1})	5.7 (2.7)	6.0 (1.5)	0.20
B-Haemoglobin (g/l)	131.0 (14.0)	134.2 (11.2)	0.28
B-Thrombocytes (10^9L^{-1})	253.4 (135.3)	250.0 (51.9)	0.38
Serum C3 (g/L)	0.90 (0.31)	1.04 (0.20)	0.008
Serum C4 (g/L)	0.14 (0.09)	0.22 (0.06)	<0.001
Serum CH50 (unit/mL)	53.5 (24.3)	70.3 (17.4)	<0.001
ESR (mm/h)	23.2 (16.3)	9.0 (6.3)	<0.001
Anti-dsDNA(U/L)	159.4 (238.0)	40.2 (1.8)	<0.001
ANA	1258.3 (1042.4)	90.4 (49.5)	<0.001
ACL	12.9 (24.5)	2.3 (8.42)	<0.001

Abbreviations: MMP-9, matrix metalloproteinase-9; C3, C4 and CH50, complement levels; ESR, erythrocyte sedimentation rate; anti-dsDNA, anti-double stranded DNA antibodies; ANA, antinuclear antibodies; aCL, IgG type anticardiolipin antibodies. *Statistics:Mann-Whitney U Test

5.1 Correlation of MMP-9 with serological indicators of disease activity

Correlations between serological indicators of disease activity and MMP-9 levels in SLE patients and controls were measured (Table 3. in study III). A highly significant positive correlation was observed between serum MMP-9 levels and leucocytes both in patients and in controls ($p < 0.0001$ for both) and a significant negative correlation between serum MMP-9 levels and levels of anti-dsDNA and ANA in SLE patients. No significant correlation of serum MMP-9 with aCL was detected.

A highly significant negative correlation was observed between serum ANA and a leucosytes (p=0.001) and a significant correlation between serum dsDNA and leucosytes (p=0.034).

5.2. Association of serum MMP-9 levels with NP manifestations

The relationship between concentrations of serum MMP-9 and NP manifestations in 44 patients with SLE was investigated (Table 16). The mean serum MMP-9 level in NPSLE patients (n=20) was 73.2 ±46.1 μg/l. and 42.8 ± 26.8 μg/l in non-NPSLE patients (n=24); the difference between mean values was statistically significant (p=0.009) (Figure 1. in study III). When evaluating serum MMP-9 concentrations in respect to different NP manifestations, the levels were significantly higher in patients diagnosed to be cognitively impaired (80.8±45.8 μg/l) than in those with normal cognitive function (48.6±34.2 μg/l; p=0.027). In other NP syndromes, no statistically significant higher or lower concentrations of MMP-9 were identified (Table 4. in study III). In SLE patients with polyneuropathy, mean serum MMP-9 levels were twice as high as in patients without polyneuropathy (106.2 μg/l versus 53.0 μg/l), but probably due to the small number of patients, the result did not reach statistical significance (p=0.087). This was also note in a single SLE patient with a demyelinating syndrome who had almost a threefold serum concentration of MMP-9 compared with patients without this demyelinating syndrome (137.8 μg/l versus 54.8 μg/l, p=0.136).

5.3. Association of serum MMP-9 levels with lupus disease activity and neuropsychiatric damage index

Regression analysis to examine associations between levels of serum MMP-9 and SLE disease activity and NP damage indexes was performed. The mean ECLAM score was 1.6 (range 0 to 5) indicating a very low disease activity. There was no significant relationship between individual MMP-9 levels and ECLAM scores in ANOVA. The mean NP-SLICC damage value was also low, 0.57±1.00. Unlike in ECLAM index, high serum MMP-9 levels tended to correlate with high NP-SLICC damage indeces, reaching a statistical significance in ANOVA (p=0.048).

5.4. Association of serum levels of MMP-9 with treatment status

The relationship between serum MMP-9 activity and treatment modalities in patients with SLE was investigated. No significant differences in serum levels of MMP-9 were found between the patients receiving either glucocorticoids or other immunomodulatory treatment and those who were not on any immunosuppressive treatment. Likewise, no significant correlation was observed between a cumulative lifetime dose of glucocorticoids and serum MMP-9 levels.

5.5. Correlation of serum MMP-9 levels with MRI parameters

In SLE patients, a positive significant correlation was observed both between the levels of serum MMP-9 and T1-lesions (r=0.33, p=0.031) and between the levels of serum MMP-9 and T2-lesions (r=0.37, p=0.015). No association was detected between the levels of serum MMP-9 and relative intracranial CSF space volume (Table 16.). In healthy controls, no correlations between levels of serum MMP-9 and MRI parametres were found**.**

Table 16. Correlation of matrix metalloproteinase-9 values with quantitative magnetic resonance imaging (MRI) volumes in patients with SLE.

MRI- parameter	R	p *
T1-weighted volume, (cm^3)	0.33	0.031
T2-weighted volume, (cm^3)	0.371	0.015
Relative intracranial CSF space volume	0.092	0.564

Abbreviations: CSF, cerebrospinal fluid.

*Statistics: Spearman’s rank order correlation test.

DISCUSSION

1. NP manifestations in patients with SLE

All neuropsychiatric manifestations

In this population-based study of 46 SLE patients, 91% were identified to have at least one NP syndrome. In previous studies, the prevalence of NPSLE has been significantly lower with psychiatric disorders and epileptic seizures being the most frequent NP manifestations (Estes & Christian 1971; Feinglas et al 1976; Gibson & Myers 1976; Grigor et al 1987; Sibley et al 1992). The impact of those early works resulted in the selection of psychosis and epileptic seizures to represent neurological involvement as a part of the original diagnostic criteria for SLE.

The main reason for the exceptionally high prevalence of NP involvement in this study may be that the ACR nomenclature and case definitions used as the basis of the classification of NP syndromes, includes a wide array of different neurological and psychiatric features. In most former studies the diagnosis of NPSLE was entirely based on major neurologic and psychiatric involvement, including cerebrovascular event, neuropathy, movement disorder, transverse myelitis, epileptic seizures, meningitis, organic brain syndrome and psychosis. In addition to these clinical syndromes, patients with SLE present with a number of minor neurologic and psychiatric problems. Although being now included in the ACR nomenclature, there is no unanimous agreement among investigators whether all these minor complications should be counted as manifestations of NPSLE or not.

This study was the first one to utilize the ACR nomenclature, but later some studies based on it have been published. In their longitudinal study, Brey et al evaluated 128 unselected patients with SLE. The subjects had a mean age and a mean educational level similar to ours, but mean disease duration was lower. Investigators discovered one or more NPSLE syndromes in 80% of the patients. The ACR standardized neuropsychological testing was performed in a subset of 67 patients. As in our study, the three most common neuropsychiatric symptoms in this cohort were cognitive dysfunction (79%), headache (57%), and psychiatric disorders (Brey et al 2002). In a study by Afeltra et al, NPSLE was found in 72% of 61 SLE patients; the most common NP manifestation was again cognitive dysfunction in half of the patients, followed by mood disorders (27%), cerebrovascular disease (24%) and headache (21%). When patients with mild deficits were not

considered, the prevalence of cognitive dysfunction was decreased to 21%. Prevalence of NPSLE was significantly higher in patients with APS (Afeltra et al 2003). In a retrospective review of 323 consecutive patients with SLE, 185 (57%) had NP manifestations according to the ACR nomenclature (Sanna et al 2003). In a study by Hanly et al, the prevalence of NP disease in an unselected cohort of 111 SLE patients was 37% (Hanly et al 2004). In both of these latter studies, headache was the most frequent NP manifestation. In summary, the minor NP manifestations are predominant NP features in newer studies based on the ACR nomenclature.

Another important difference between this study and the former works is the patient selection. No other population-based study on the prevalence of NPSLE has been published so far. In the previous studies patients have been gathered from academic referral centers, which is likely to be biased in terms of disease severity in comparison with the general population. Furthermore, with the advent of more sensitive diagnostic tests and accompanying greater awareness of SLE, much milder forms of the disease are now being recognized than were a few decades ago. Especially the availability of standardized neuropsychological assessment technique has highlighted the awareness of cognitive deficits (Sibley et al 1992; Hanly et al 1997). Unexpectedly, the total amount of NP manifestations in our work was higher than in older ones, but this fact can mainly be explicated by the use of ACR nomenclature as the basis of classification. The greater amount of minor NP manifestations, especially cognitive dysfunction must be associated with more sensitive diagnostic testing.

Cognitive impairment

Cognitive impairment was the most frequent finding occurring in 37 (80%) patients. Previously reported prevalence rates have been lower, ranging between 21-66% (Carbotte et al 1986; Hay et al 1992; Hanly et al 1992; Ginsburg et al 1992; Hanly et al 1994; Hanly et al 1997). This may be partly explained by the higher mean age and longer disease duration of our patients than in the previous studies. Furthermore, the battery of neuropsychological tests carried out by us was extensive, requiring up to 3 hours to complete, compared to for example 1,5 h in some studies (Hanly et al 1992) The most plausible explanation, however, pertains to the criteria of cognitive impairment. According to the ACR nomenclature, individual patients were defined as cognitively impaired if they demonstrated impairment in one or more of eight areas of cognitive ability. In 70% of our patients with cognitive impairment, the dysfunction was classified as mild, implying that the impairment was established in only one or two cognitive domains. Eleven patients had three or

more impaired areas, fulfilling the criteria for cognitive impairment used by Hanly et al. Based on this definition, only 24% of our study population would have been classified as having a cognitive impairment. This figure is in accordance with prevalence rates of 21% in a study of 70 unselected SLE patients and 26% in a study of 73 patients (Hanly et al 1992; Hay et al 1992).

In the newer studies based on the ACR nomenclature system, the prevalence of cognitive impairment has varied between 3% and 79%. Brey et al found that cognitive dysfunction, detected by a battery of neuropsychological tests done in half of the patients, was the most frequent single NPSLE manifestation, with an overall prevalence of 79% but severe impairment was seen only in 6% of the patients (Brey et al 2002). According to the Italian study including 61 SLE patients who all received neuropsychological testing, the prevalence of cognitive impairment was 52% (Afeltra et al 2003). In a Canadian study only three of 111 patients with SLE were found to have cognitive deficits. Neuropsychological testing, however was done only if indicated following clinical assessment (in six patients) (Hanly et al 2004). The lack of routinely used neuropsychological testing is supposed to lead to underestimate the actual prevalence rate of cognitive impairment and simultaneously the overall frequency of NP disease. This statement is supported by the finding that only 38% of our patients with cognitive dysfunction in neuropsychological tests complained of cognitive problems.

Headache

In this study population, 25 patients (54%) had suffered from headache, with a life-time prevalence of migraine and tension headache being 39% and 15%, respectively. In former studies, the prevalence of migraine in SLE has varied from 34% to 40% (Omdal et al 1988; Vazques-Cruz et al 1990; Markus & Hopkinson 1992), but two studies found no difference in the occurrence of headache between SLE patients and matched controls (Sfikakis et al 1998; Ferdandez-Nebro et al 1999). In a study by Brey, the prevalence rate of 57% was near ours (Brey et al 2002). There is controversy concerning headache as a NP manifestation. Episodes of migraine attacks have been reported to parallel the systemic disease activity in some patients (Brandt & Lessel 1978; Abel et al 1980; Appenzeller & Costallat 2004), but they have also been associated with psychological distress and social problems (Sfikakis et al 1998; Waterloo et al 2000)

Psychiatric manifestations

There is a wide variation in the reported prevalence of psychiatric manifestations. The majority of recent reports on NPSLE have focused on the occurrence of milder psychiatric features such as depression and anxiety, whereas, in contrast to older studies, low prevalence of psychosis has been noticed (Sibley et al 1992; Hay et al 1992). These results corroborate this finding: 80% of patients with mood disorder had mild depression requiring no medication, while nobody had experienced any episode of psychosis. In a study by Brey, the presence of psychiatric manifestations was common (74%), although past or current psychosis was rare (Brey et al 2002). So far, no consensus exists whether the minor psychiatric manifestations represent primary NPSLE.

Cerebrovascular disease

Cerebrovascular disease was diagnosed in seven (15%) of SLE patients. In other studies based on the ACR nomenclature, the frequency of cerebrovascular disease has varied from 2% to 18%, these rates are in accordance with older studies (Estes & Christian 1971; Feinglas et al 1976, Gibson & Myers 1976; Grigor et al 1987; Sibley et al 1992; Brey et al 2002; Sanna et al 2003; Hanly et al 2004). Patients with SLE who have had a stroke or TIA are at high risk, up to 57%, for recurrent cerebral ischemia (Futrell et al 1992). Two of seven patients with cerebrovascular disease had a recurrence of stroke or TIA and one had a chronic multifocal disease. Previously it has been reported that the major period of risk for the first stroke is during the first five years of SLE (Futrell & Millikan 1989) but in our patients with cerebrovascular disease, range of time between the diagnosis of SLE and the first cerebrovascular attack was 1-18 years with the mean of 10.7 years. A significantly higher cumulative lifetime dose of steroids in SLE patients with a history of cerebrovascular disease obviously reflects the serious character of this subgroup.

Neuropathy

A mild, symmetrical distal sensory or sensorimotor neuropathy is the most common form of peripheral neuropathies in SLE. A 28% frequency of polyneuropathy in the present study is certainly overestimated, and greatly influenced by the fact that the ACR nomenclature system does not demand an ENMG confirmation of polyneuropathy. The corresponding prevalence of ENMG confirmed polyneuropathy in this series was 7%, being in accordance with the previous studies and near the prevalence rates in newer studies by Sanna and Costallat (2-3%) (Estes & Christian 1971;

Feinglass et al 1976; Gibson & Myers 1976; Grigor et al 1978; Omdal et al 1988; Hietaharju et al 1993; Sanna et al 2002; Costallat et al 2001). In a study by Brey, the prevalence rate without ENMG confirmation was higher, 22% (Brey et al 2002). Becauce no quantitative sensory testing was performed in our study, there exists a possibility of small fiber polyneuropathy in patients with normal ENMG findings. If taken into consideration that only one of these patients had symptoms correlating with polyneuropathy, it can be assumed, that at least the majority of them had no neuropathy at all.

Demyelinating syndrome

One of the patients fulfilled the ACR nomenclature criteria for a demyelinating syndrome. A diagnosis of MS had been established, but it is assumed that the true cause for her neurological symptoms was APS. APS is defined by the persistent presence of APA in patients with recurrent venous or arterial thromboembolism or pregnancy morbidity. It can occasionally mimic MS (Scott et al 1994; Cuadrado et al 2000). This patient had neurological and MRI findings similar to MS, but a high positive titer of aCL together with the history of thrombocytopenia and deep venous thrombosis strongly favors the diagnosis of APS. Oligoclonal banding has been described to occur in patients with secondary APS due to SLE (Cuadrado et al 1994). It is to be recommended that future revisions of the ACR nomenclature system specifically exclude APS in the diagnosis of a demyelinating syndrome.

2. Validity of the ACR nomenclature and case definitions

In this population-based material, the ACR criteria and case definitions for NPSLE had a low specificity, i.e. they were not able to differentiate SLE patients from controls. Ideally, case definitions should be based on SLE activity in the nervous system manifested as neurologic dysfunction (Moore & Lisak 1995). No underlying neurologic dysfunction, however, has been demonstrated for several syndromes listed under case definitions in the current ACR nomenclature for NPSLE. A more stringent set of criteria based solely on manifestations of neurologic injury is proposed.

Signs of minor CNS dysfunction were frequent among both SLE patients and controls, which led to poor specificity and lack of distinction between the two groups. For example, it is very difficult to justify the inclusion of headaches: although they were more common among cases than controls

(54% vs. 24%), the high prevalence among controls did not allow distinction between NPSLE and other conditions manifesting as headache. It has been reported that up to 40% of individuals experience severe disabling headache at least one per year (Jennekens & Kater 2002). In a Norwegian study, headaches were not associated with SLE disease activity (Waterloo et al 2000). Tension-type headache in SLE patients was associated with psychological distress and depressive mood, while migraine was associated only with a tendency to social isolation and anxiety. Thus, although headache might be a component of active SLE in individual patients, it is more likely that the majority of headaches in SLE patients are due to non-SLE causes. Furthermore, ACR case definitions do not include EMG for diagnosing polyneuropathy. The results of this study, with more than 10% of controls presenting with sensory or motor symptoms, indicate that subjective symptoms are too vague and unspecific and EMG confirmation is required to demonstrate neurologic injury.

Despite its frequency, mild cognitive dysfunction was not specific for NPSLE as it was also detected in a quarter of controls. According to ACR case definitions, documented impairment in one of the cognitive domains is sufficient for the diagnosis of cognitive dysfunction. Previously, it has been proposed that the minimum of three impaired domains are required (Hanly et al 1992). Results of this study indicate that this is required for detecting clinically relevant neuropsychological defect.

Mild depression and anxiety are common in otherwise healthy subjects and even more so among patients with chronic diseases (Patton et al 1999, Soderlin et al 2000). They can be regarded as psychological responses to illness and therefore are not specific for NPSLE (Rogers et al 1996). Functional brain imaging techniques have demonstrated that major depression is associated with both reversible and irreversible neurophysiological abnormalities in some structures (Drevets 1998). An association to APL and anti-ribosomal-P-antibodies has also been found (Arnett et al 1996). Major depression can be considered analogous to psychosis in psychiatric morbidity, and its inclusion in the diagnostic criteria for NPSLE is justified.

The results of this study demonstrate inadequate performance of the proposed ACR criteria. It appears that there are no pathognomic manifestations, but NPSLE has shared features with other CNS conditions. Therefore, revised criteria are needed to distinct NPSLE from other conditions. Discriminating accurately between NP manifestations truly attributable to SLE is of highest importance to achieve homogenous patient subsets, a prerequisite for studies focused on

pathogenesis. We derived criteria based on neurologic injury or dysfunction and excluded conditions that may not indicate a neurologic dysfunction. Higher correlation of SLICC with the revised criteria than ACR criteria lends further credence to our approach. To support the basis of classification, further research on organic nervous system damage with pathogenetic mechanisms specific to SLE is warranted.

Our revised criteria for NPSLE have already been used in an international inception cohort study, in which 572 patients with SLE were enrolled within 15 months after having fulfilled the ACR SLE classification criteria. All NP events were identified using the ACR case definitions. Decision rules were derived to determine the proportion of NP disease attributable to SLE, and onset of an NP event prior to the enrollment window, the identification of at least one non-SLE factor or the occurrence of minor NP events defined by our study classified the NP event as not attributable to SLE. The results indicate that 158 patients (28%) had at least one NP event around the time of diagnosis of SLE, of which only a minority (19%-38%) were attributed to SLE. However, formal neuropsychological assessments were not performed routinely on all patients and the 5.4% prevalence of cognitive dysfunction suggests an underestimation of clinically important cognitive disorders. An interesting finding in this study was that regardless of attribution, the occurrence of NP events in these newly diagnosed patients was associated with reduced quality of life and increased organ damage (Hanly et al 2007).

Jennekens and Kater have systematically searched the literature from 1980 to 2002 for CNS manifestations in SLE. The syndromes found were evaluated with the authors´ inclusion criteria for SLE attribution. They ended up with 16 syndromes and compared their findings with the ACR case definitions. They consider as a disadvantage of the ACR system the concealment of differences in health risks by pooling the items. Furthermore, the items of the system do not all belong to the same dimension; one is pathological and the others are clinical. The authors have proposed a modification of the ACR nomenclature system. Migraine is left out since the investigators cannot find any support for SLE induction. Anxiety and mood disorder have been included to the modified system but they should be handled separately, since they are likely to be predominantly psychoreactive in many patients though, in some cases, there may be a role for biological factors. Acute confusional state is replaced by delirium, as this term is used by DSM-IV. Demyelination syndrome is replaced by “myelopathy and optic neuropathy (Devic`s syndrome)” which refers to clinical syndromes in contrast to demyelination syndrome, which has no clear clinical annotation. (Jennekens & Kater 2002).

Despite of its deficiency, the ACR nomeclature is a step into the right direction in evaluating SLE patients with NP disorders. These criteria will certainly increase the consistency in the classification of patients and standardize clinical descriptions in clinical research. The identification and categorization of the major neurological and psychiatric syndromes in SLE seems to be adequate. It is hoped that in future the understanding of mechanisms of the minor NP manifestations will be improved, leading to more precise formulation of the classification criteria of NPSLE.

3. Neuroradiological findings in patients with NPSLE

Brain atrophy

SLE patients had more evidence of cerebral atrophy in MRI scans than the controls, this result supports previous findings (McCune & Golbus 1988; Chinn et al 1997; Kozora et al 1998). The aetiology of cerebral atrophy in SLE patients is unknown. It has been suggested to reflect an ongoing CNS involvement, to result from a long-standing glucocorticoid use, or to be a combination of both of these processes (Kovacs et al 1993). In our SLE patients, a clear correlation was detected between cerebral atrophy and the cumulative dose of glucocorticoids but the current use of glucocorticoids or any other medication was unrelated with atrophic changes. Chinn et al (Chinn et al 1997) found no association between either the current or past use of steroids or the total amount of steroid used and the presence of atrophy in 47 SLE patients, but in another study, a trend for significant relationship between cerebral atrophy and prednisone dose was observed (Kozora et al 1998). In recent studies, Appenzeller and colleagues detected no association between the total corticosteroid use and cerebral and corpus callosum volumes in adult SLE patients but an association with hippocampal atrophy was found (Appenzeller et al 2005, Appenzeller et al 2006). Brain MRI abnormalities were recently reported in a consecutive cohort of 97 SLE patients enrolled within 9 months of diagnosis. Brain atrophy was seen in 18% of patients, which suggests that the brain may be affected early in the course of SLE. Although perhaps worsened by high cumulative corticosteroid use, the development of brain atrophy may not be dependent of it (Muscal & Brey 2010).

It has been speculated whether cerebral atrophy is responsible for some of the NP manifestations related to SLE (Kovacs et al 1993). In this study, the patients with NPSLE had higher volumes

indicating cerebral atrophy than the patients without NPSLE. Furthermore, cerebral atrophy was increased in SLE patients with cognitive dysfunction, cerebrovascular disease and seizure disorder compared with SLE patients without these NP manifestations. Previously, no correlation has been demonstrated between quantitative measures of non-specific abnormalities in cerebral MRI and measures of brain function. Kozora et al found no association between cerebral lesions measured by quantified MRI analyses and functional abnormalities determined by comprehensive neuropsychological testing in 20 SLE patients without overt central nervous system disease (Kozora et al 1998). After our work, in one study a reduction in cerebral and corpus callosum volumes was demonstrated to associate with cognitive impairment and other CNS manifestations (Appenzeller et al 2005). Our results are also in accordance with a study by Bosma et al, in which the presence of cognitive dysfunction and psychiatric abnormalities in a sample of 24 patients with NPSLE correlated with cerebral atrophy. This study utilized a new sensitive MRI technique, volumetric magnetic transfer imaging (MTI). Contrary to the findings of this study, the results did not indicate a relationship between duration of SLE and cerebral atrophy (Bosma et al 2002)

T1- and T2-weighted lesions

In our study, the volumes of both T1- and T2-weighted lesions were significantly higher in SLE patients than in controls. Similarly, NPSLE patients had increased volumes of both lesion types in comparison with non-NPSLE patients. T1-weighted lesions included only gliotic infarcts and gliotic demyelinating lesions, T2-weighted ones also microinfarcts, ischemic lesions and non-gliotic demyelinating lesions. It is generally known, that T2-weighted images of the brain reveal in many SLE patients small punctate lesions localized mainly in the periventricular and subcortical white matter. These lesions may represent small-vessel vasculopathy, which has been suggested to be a pathogenetic mechanism in those SLE patients who have cognitive disorder as a sole neuropsychiatric manifestation (Jennekens & Kater 2002). Our results support this hypothesis since volumes of T2-weighted lesions were statistically significantly higher in SLE patients with cognitive dysfunction than those without. On the other hand, the volumes of T1-weighted lesions representing gross infarcts did not have an association with cognitive impairment.

Correlations to ECLAM and SLICC

SLE activity index ECLAM score did not correlate with any of the MRI parameters. In two previous studies, such correlation has been noticed (Cauli et al 1994; Taccari et al 1994). The

opposite findings may be due to considerably low ECLAM scores in SLE patients of this study, since most of them were in good health at the time of the assessment. Instead, neuropsychiatric SLICC damage index score correlated positively with all the measured MRI parameters. This is in accordance with the results of Sanna et al, demonstrating the presence of significantly higher values of SLICC score in patients with abnormal brain MRI (Sanna et al 2000). Of other clinical features, person's age correlated positively with the volumes of T2-weighted lesions both in patients and in controls.

The present study confirms in a population-based sample that both brain atrophy and occurrence of gliotic infarcts, microinfarcts, other ischemic lesions and demyelinating lesions were significantly more common in patients with SLE than in general population. Second, previous studies have not been able to show any relationship between cerebral MRI abnormalities and specific neuropsychiatric dysfunctions. In this study, cerebral atrophy correlated with cognitive dysfunction, cerebrovascular disease and seizure disorder. Contrary to other findings, a clear correlation was also detected between cerebral atrophy and the cumulative use of corticosteroids.

4. Serum levels of MMP-9 in patients with NPSLE

MMPs are a family of zinc-containing endo-proteinases produced by a variety of inflammatory cells. All of the cell types that exist in the CNS are potential sources of MMPs. (Lijnen 2001; Trysberg & Tarkowski 2002). The growing list of MMPs is currently grouped into collagenases, gelatinases, stromelysins and membrane-type MMPs (Cuzner & Opdenakker 1999). So far, a total of 22 human MMPs have been identified (Kalela 2002).

MMPs can degrade a variety of extracellular matrix components (Lijnen 2001). They have a multitude of regulatory functions, including control of influx of inflammatory mononuclear cells into the CNS, participation in myelin destruction and disruption of the integrity of the blood-brain barrier (Trysberg & Tarkowski 2004). The extracellular matrix alterations mediated by MMPs are critical for normal development and tissue homeostasis but they are also central to a range of pathological processes (Sobel 2001). Increased activity of MMPs has been implicated in numerous disease processes including malignancies, cardiovascular diseases and autoimmune diseases such as multiple sclerosis, Guillain-Barré syndrome, and rheumatoid arthritis (Gijbles et al 1992; Ahrens et

al 1996; Zucker et al. 1999; Lee et al 1999; Cuzner & Opdenakker 1999; Creange et al 1999; Kalela et al 2002).

Serum levels of MMP-9

In the present study, the serum levels of MMP-9 were analyzed. No significant difference in the consentration of serum MMP-9 was found in SLE patients and controls. This finding is not in accordance with a previous study, which showed a significant increase of MMP-9 activity in the sera of 40 SLE patients compared with 25 healthy controls (Faber-Elmann et al 2002). However, our patients with NPSLE had significantly higher levels of serum MMP-9 than the patients without. In addition, a positive correlation of serum MMP-9 levels with NP-SLICC index was detected. These two observations corroborate the primary hypothesis according to which MMP-9 levels may reflect CNS injury in SLE patients.

Our results are supported by a recent study by Trysberg et al, in which intrathecal MMP-9 levels were determined in 123 patients with SLE. Intrathecal MMP-9 levels were significantly increased in patients with NPSLE compared with SLE patients without CNS involvement. In this study, significant correlations between MMP-9 and intrathecal levels of neuronal and glial degradation products were also noted, indicating ongoing intrathecal degeneration in the brains of SLE patients expressing MMP-9 (Trysberg et al 2004).

MMP-9 and ECLAM

It has been speculated upon whether MMPs are related to disease activity in SLE or not. In a previous study, a positive correlation between MMP-9 concentration and disease activity scores was observed but only in men (Faber-Elman et al 2002). In this study, no association between MMP-9 levels and ECLAM scores was found in either sex. This may be partly explained by that at the time of the assessment, the majority of our patients were in good health and, as a consequence, the ECLAM scores in general were not high. In fact, if the levels of MMP-9 truly parallel the disease activity, they would be expected to be low in our patients.

MMP-9 and vasculopathy

Cerebral small-vessel vasculopathy has been suggested to underlie the cognitive disorder in SLE (Jennekens & Kater 2002); present findings support the hypothesis since volumes of T2-weighted lesions were statistically significantly higher in SLE patients with cognitive dysfunction than in those without. Moreover, the patients with cognitive deficits had higher serum concentrations of MMP-9 than patients who had normal cognitive functions. In addition, in SLE patients, serum MMP-9 levels associated with T1- and T2-hyperintensities in MRI scans. These findings tempt us to speculate that MMP-9 concentration relates to the underlying pathological process, small-vessel vasculopathy. The pathogenesis of vasculopathy in the brain is not clear (Jennekens & Kater 2002). The finding of the association between leucocyte count and serum MMP-9 concentration in both SLE patients and in healthy controls confirms previous reports by Kalela et al. and supports the concept of MMP-9 being a useful marker of inflammation (Kalela et al 2000). Furthermore, these findings may indicate that there is an inflammatory process behind small angiopathic changes in the brain of SLE patients. The elevated MMP-9 levels in SLE patients with cognitive dysfunction may reflect an ongoing active process, since elevated plasma MMP-9 concentrations after acute coronary syndromes and successful reperfusion of acute myocardial infarction are reversible and gradually decrease to the level of normal control subjects (Kalela et al 2002; Hirohata et al 1997; Kai et al 1998).

MMP-9 in neurological diseases

This study was the first to investigate the correlation of serum MMP-9 concentration with MRI abnormalities in SLE, but the results are in agreement with former studies of MMP-9 levels, which have shown increase of MMP activity in patients with stroke and vascular dementia i.e., clinical states associated with vasculopathy (Hughes et al 1998; Rosenberg et al 2001). In line with present findings in SLE patients, a significant positive correlation between high serum levels of MMP-9 and the number of T1-weighted gadolinium-enhancing MRI lesions in MS patients has been reported (Lee et al 1999). Increased CSF and serum levels of MMP-9 in patients with MS and expression of MMP-9 in demyelinating lesions have suggested that MMPs may have importance in the pathogenesis of this disease (Gijbles et al 1992; Lee et al 1999; Cuzner et al 1999). MMP-9 has also been related to other autoimmune disorders such as Guillain-Barré syndrome and experimental autoimmune neuritis (Hughes et al 1998; Creange et al 1999). In relation to these diseases, it has been assumed that MMP-9 participates in degradation of myelin basic protein, a major component

of both CNS and peripheral nervous system myelin (Creange et al 1999). Interestingly, demyelinating syndrome, which may clinically resemble MS, is listed as one of the manifestations of NPSLE. In this study, one of the patients was diagnosed to have a demyelinating syndrome and she had a high consentration of MMP-9.

This study is the first one to evaluate MMP-9 concentration in NPSLE. It suggests that elevated levels of serum MMP-9 in patients with SLE may indicate NP involvement. Thus, a determination of serum MMP-9 level may be a useful tool in follow-up of these patients and give support to the clinical suspicion of NPSLE. High serum levels of MMP-9 in a SLE patient should keep the clinicians on the alert for small-vessel cerebral vasculopathy and prompt them to evaluate the presence of additional stroke risk factors and need for possible therapeutic measures. A tendency to cognitive dysfunction in SLE patients with high MMP-9 concentration should also be taken into consideration.

Study limitations

This case series consisted of a population-based prevalence sample of SLE patients; a need for this kind of study design has widely been recognized. The participation rate of 78% in this study is very good. Prevalence sampling has a disadvantage of selecting less severe cases with favorable prognosis (Rothman & Greenland 1998). In present study, however, both deceased subjects and non-participants had a lower mean ACR score than participants, indicating lack of selection by severity. The differences between evaluated patients and eligible patients who could not be enrolled were small and are not likely to substantially effect the results.

The lifetime incidence of the various syndromes may be skewed by the intensive search for cognitive syndromes contrasted with the less intensive search for subtle cerebral infarcts. In our study, however, we tried to follow the ACR case definitions as accurately as possible and, as stated by ACR on cerebrovascular disease, “the finding of unidentified bright objects on MRI without clinical manifestation is not classified at the present time”. On the other hand, ACR definitions imply that all eight cognitive domains should be included in neuropsychological tests.

The main weakness of the study is a small sample size and therefore the results need to be interpreted with caution. As a cross-sectional study, the validity of disease history depends on the documentation of past disease episodes. It is assumed, that this is unlikely to have a substantial effect on the prevalence rates of the NP syndromes, but reliable discrimination between primary NPSLE (i.e. caused by immune-mediated direct or indirect effects), secondary NPSLE and concurrent disease process becomes problematic. It has been estimated that two thirds of NP manifestations in SLE are not directly related to primary NPSLE, but to secondary causes such as drugs, infections and metabolic complications of the disease (secondary NPSLE) (Kovacs et al 1993; Moore & Lisak 1995). Prospective analyses would help in discriminating between primary and secondary NPSLE.

A study base was defined and all prevalent cases of SLE and population-based controls in it were identified. Matching for age, sex and education was used to maximize comparability between cases and controls, as well as to minimize loss of information. Ideally, the performance of a diagnostic test is assessed against a golden standard revealing the true disease status. However, as no golden standard is available for determining the presence of NPSLE, SLE was used as a surrogate measure of NPSLE. This is justified by the fact that in a case-control study, specificity in case ascertainment is more important than sensitivity, as it results in loss of statistical power, but does not bias the results (Drevets et al 1998). Lack of golden standard is likely to underestimate the sensitivity as the reference is SLE patients, all of whom do not have NPSLE. Small sample size limited the statistical power of the analyses, therefore rare syndromes as manifestations of NPSLE could not be assessed in this material. Further studies with larger patient populations are likely to reveal more subtle differences between SLE patients and controls.

SUMMARY AND CONCLUSIONS

1. At least one NP syndrome was identified in 91% of SLE patients in this population-based study. The most frequent single manifestation was cognitive dysfunction followed by headache and mood disorder. When mild NP syndromes (mild cognitive deficit, headache, mild depression, anxiety and polyneuropathy with normal ENMG findings) were excluded, the prevalence of NPSLE dropped to 46%.

2. The proposed 19 ACR criteria for NPSLE are neither able to differentiate SLE patients from controls nor NPSLE patients from non-NPLSE patients. New revised criteria based on neurologic injury and dysfunction were derived and they performed well in this study population.

3. Brain atrophy, cerebrovascular and demyelinating lesions are significantly more common in patients with SLE than in general population. Cerebral atrophy in SLE patients is associated with cognitive dysfunction, cerebrovascular disease and seizure disorder. There is a connection between cerebral atrophy and the cumulative dose of glucocorticoids in patients with SLE.

4. Elevated levels of serum MMP-9 in patients with SLE may indicate NP involvement, especially cognitive dysfunction. A determination of serum MMP-9 level can be a useful tool in follow-up of SLE patients and give support to the clinical suspicion of NPSLE. High serum levels of MMP-9 in SLE patients may reflect small-vessel cerebral vasculopathy and should prompt the clinicians to evaluate the presence of additional stroke risk factors and need for possible therapeutic measures.

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The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus

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Article abstract—*Objective:* To describe the prevalence of neuropsychiatric (NP) syndromes in a Finnish population of patients with systemic lupus erythematosus (SLE) and to classify them according to the recently developed American College of Rheumatology (ACR) nomenclature and case definitions for NPSLE. *Methods:* Cross-sectional, population-based study covering an area with 440,000 people. A total of 58 patients with a definite diagnosis of SLE and aged 16 to 65 years were found in the computerized database of the area hospitals. Of these, 46 (79%) agreed to participate. The diagnosis of various NP syndromes was based on clinical impression (H.A.) following history, examination, review of medical records, and neuropsychologic testing. *Results:* At least one NP syndrome was identified in 42 patients (91%). The most frequent manifestation was cognitive dysfunction (n = 37; 81%), followed by headache (n = 25; 54%) and mood disorder (n = 20; 43%). When mild NP syndromes (mild cognitive deficit, headache, mild depression, anxiety, electroneuromyography-negative polyneuropathy) were excluded, the prevalence of NPSLE dropped to 46%. *Conclusions:* According to the ACR nomenclature, there is a high prevalence of NP manifestations in a population-based sample of patients with SLE. Most NP syndromes were classified as minor; if they were excluded, the 46% prevalence of NPSLE would be slightly less than estimated in previous studies.

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A challenging problem in systemic lupus erythematosus (SLE) is the diagnosis and management of neuropsychiatric (NP) involvement. NPSLE may present with serious manifestations (e.g., acute confusional state, seizure disorder, and stroke), but more subtle deficits such as mild cognitive dysfunction have also been recognized.[1,2] The prevalence of NPSLE ranges widely between 14 and 75%, reflecting variable diagnostic criteria and differences in selection of patients for study.[3,4] A former definition for NPSLE in the 1982 revised American College of Rheumatology (ACR) criteria for SLE is inadequate because only two elements, psychosis and seizures, were included.[5] The ACR has recently developed a standardized nomenclature system which provides case definitions for 19 NP syndromes seen in SLE, including reporting standards and recommendations for laboratory and imaging tests.[6]

We studied the prevalence of NP syndromes in a Finnish population-based cohort of patients with SLE and classified the syndromes according to the ACR nomenclature and case definitions.

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Patients and methods. *Patient selection.* The study base was Pirkanmaa Health Care District located in southern Finland with a population of 440,000. The majority of new patients with SLE in the area are seen at Tampere University Hospital. We identified patients with SLE using the computerized databases of Tampere University Hospital, the three District Hospitals, and the local outpatient clinic. Medical records of both in- and outpatients coded for the diagnosis of SLE between January 1980 and December 1997 were examined to select patients who fulfilled four or more of the 1982 revised ACR criteria for the disease,[5] were aged 16 to 65 years and of native Finnish origin, and resided in the study area. We excluded patients with another connective tissue disease.

We identified 110 patients with SLE. Of these,15 patients had died and 37 did not meet the inclusion criteria. The remaining 58 patients were contacted by mail, and 46 of them (79%) agreed to participate in the study. All participants gave written informed consent. The study protocol was approved by the local Ethics Committee.

Clinical and laboratory evaluation. The diagnosis of various NP syndromes was based on clinical impression (H.A.) following history, examination, review of medical records, and neuropsychologic testing. All past and current NP syndromes were listed and classified according to the standardized ACR nomenclature and case definitions[6] (table1). Individual disease activity was quantified by using

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Table 1 *The neuropsychiatric syndromes in patients with systemic lupus erythematosus according to the American College of Rheumatology nomenclature and case definitions*[3]

Central nervous system	Peripheral nervous system
Aseptic meningitis	Acute inflammatory demyelinating polyradiculoneuropathy
Cerebrovascular disease	Autonomic disorder
Demyelinating syndrome	Mononeuropathy, single/multiplex
Headache	Myasthenia gravis
Movement disorder (chorea)	Neuropathy, cranial
Myelopathy	Plexopathy
Seizure disorders	Polyneuropathy
Acute confusional state	
Anxiety disorder	
Cognitive dysfunction	
Mood disorder	
Psychosis	

the European Consensus Lupus Activity Measurement (ECLAM) scale.[7] Current and previous use of steroid and other immunosuppressive medication was recorded. Cumulative lifetime dose of steroids (expressed as grams of prednisolone) was determined from the patients' records. Electroneuromyography (ENMG) was performed on patients with clinical signs/symptoms suggesting polyneuropathy. Besides routine serological tests, IgG-type anticardiolipin antibodies (aCL) and B2-glycoprotein antibodies (B2GPAbG) were measured by ELISA (commercial kit).

Neuropsychologic measures. All patients were submitted to a battery of standardized neuropsychologic tests to detect possible impairment in one or more of the subsequent cognitive domains: simple attention, complex attention, memory, visuo-spatial processing, language, reasoning/problem solving, psychomotor speed, and executive functions. The tests were administered by a trained psychologist. It took an average of 3 to 4 hours to complete the assessment. The individual test results were converted into standard scores, which were compared with the available normative data.[8-12] Regarding any of the eight cognitive domains, subjects with a total score of two or more standard deviations (SD) below the normative value were considered to be impaired. Cognitive dysfunction was classified as mild if there were deficits in less than three dimensions, as moderate if there were deficits in three or four dimensions, and as severe if there were deficits in at least five dimensions.

Assessment of depression was based on clinical interview and the Beck Depression Inventory (BDI).[13,14] On BDI, scores from 10 to 17 were considered to indicate mild depression, from 18 to 24 moderate depression, and greater than 24 severe depression. However, the final grading of depression was based on a clinical interview by the psychologist. Anxiety was evaluated by the psychologist on clinical interview.

Statistical analysis. Pearson exact χ^2 test for cross-tabulated data, two-sample Student's *t*-test, and Mann–Whitney *U* test were used to evaluate the association between occurrence of any NP manifestation and current or prior steroid use. The limit for significance was set equal to 0.05.

Results. We studied 39 women and seven men, with a mean age of 45 ± 13 years (range 20 to 64). The mean disease duration since diagnosis of SLE was 14 ± 8 years (range 2 to 37). The mean number of ACR SLE criteria fulfilled was 5.5 ± 1.2 (range 4 to 9). The mean level of education was 13 ± 3 years (range 8 to 18). The mean ECLAM score was 1.6 (range 0 to 5), indicating a very mild disease activity. At the time of the study, 25 patients (54%) were using glucocorticoids, seven (15%) were on antimalarials, five (11%) on azathioprine, two (4%) on methotrexate, and one (2%) on cyclosporin. Nineteen patients (41%) were without specific medication. For those who had taken steroids, the mean cumulative lifetime dose of prednisolone was 26 *g* (range 1 to 89). A total of four patients (9%) had never used corticosteroids.

At least one NP syndrome was identified in 42 patients (91%). Five patients (11%) had one, 12 patients (26%) had two, 15 patients (33%) had three, four patients (9%) had four, four patients (9%) had five, and two patients (4%) had six NP syndromes, whereas only in four patients was no evidence of NP syndromes detected (table 2).

The most frequent single manifestation was cognitive dysfunction, detected in 37 patients (81%). Memory dysfunction was the most affected domain registered in 20 patients (43%), followed by deficits in simple attention, visuospatial processing, and psychomotor speed, each in 12 patients (26%). Only 14 of 37 patients (38%) with cognitive dysfunction by testing had cognitive problems. Headache was diagnosed in 25 patients (54%). Depression, consisting of a major depressive-like episode of mostly mild severity in 18 and a mood disorder with mixed features in two patients, was detected in 43% of patients. Clinical findings possibly related to polyneuropathy were detected in 13 patients, but only four patients had subjective symptoms. ENMG findings consistent with polyneuropathy were present in only three of them. Seven patients (15%) had a history of cerebrovascular disease. No intracerebral hemorrhages were recorded. Mean time since the diagnosis of SLE to the occurrence of the first stroke or transient ischemic attack was 11 years (range 1 to 18). In four patients cerebrovascular disease was concomitant with systemic disease activity.

One patient (2%) had a demyelinating syndrome. The neurologic symptoms appeared with subacute onset 18 years after the diagnosis of SLE. In CSF examination, IgG index was elevated and eight oligoclonal bands were present, indicating intrathecal synthesis. Increased signal in periventricular white matter and at the level of corona radiata on T2-weighted MRI scans was observed. Both aCL (151 IgG phospholipid unit) and B2GPAbG (333 standard IgG anti-beta 2 GPI unit) levels were in the high positive range.

There was an association between history of headache and current steroid use ($\chi^2 = 4.114$; $p = 0.043$). Compared with other patients with SLE, those with a history of epileptic seizures (mean 65.0*g* vs 23.0*g*; $t = 3.319$, $p = 0.002$) or cerebrovascular disease (mean 45.4*g* vs 22.7*g*; $t = 2.288$, $p = 0.028$) had a higher cumulative lifetime dose of steroids. No other associations between occurrence of NP manifestation and steroid use were noticed.

Table 2 *Neuropsychiatric syndromes in 46 patients with systemic lupus erythematosus*

Neuropsychiatric syndrome	n (%)
Cognitive dysfunction	37 (80)
Mild	26
Moderate	7
Severe	4
Headache	25 (54)
Migraine without aura	6
Migraine with aura	12
Tension headache	7
Mood disorders	20 (44)
Major depressive-like episode	18
Mood disorder with mixed features	2
Polyneuropathy*	13 (28)
Cerebrovascular disease†	7 (15)
Stroke syndrome	5
Transient ischemic attack	2
Chronic multifocal disease	1
Anxiety disorder	6 (13)
Seizures	4 (9)
Acute confusional state	3 (7)
Neuropathy, cranial‡	3 (7)
Aseptic meningitis	1 (2)
Demyelinating syndrome	1
Movement disorder (chorea)	1
Myasthenia gravis	1

* ENMG findings consistent with polyneuropathy in three patients only.
† One patient had had both a stroke syndrome and a transient ischemic attack.
‡ Optic neuropathy in all cases.

Discussion. In our study of 46 patients with SLE, 91% were identified to have at least one NP syndrome, whereas in previous studies, the prevalence of NPSLE was significantly lower, ranging from 14 to 75%.[15-20]

The main explanation for the exceptionally high prevalence of NP involvement in our study is most likely that the ACR nomenclature system includes a wide array of different neurologic and psychiatric features as diagnostic elements. In most former studies the diagnosis of NPSLE was entirely based on major neurologic and psychiatric involvement, such as cerebrovascular event, neuropathy, movement disorder, transverse myelitis, seizure, meningitis, organic brain syndrome, and psychosis.[15-16] Patients with SLE also present with a number of minor neurologic and psychiatric problems such as headache, mild depression, anxiety, and cognitive complaints that have now been included in the new nomenclature system. If these minor manifestations and also ENMG-negative polyneuropathy were excluded, the prevalence of NPSLE in our series would be 46% instead of 91%.

Another important difference compared with former studies is in patient selection. To our knowledge, no population-based study on the prevalence of NPSLE has been published so far. In the previous studies patients have been gathered from academic referral centers likely to be biased in terms of disease severity in comparison with the general population. Furthermore, much milder forms of the disease are now being recognized than a few decades ago.[20]

Cognitive impairment was the most frequent finding, occurring in 37 patients (80%). Previously reported prevalence rates have been lower, ranging from 21 to 66%.[2,21-26] According to the ACR nomenclature, individual patients were defined as cognitively impaired if they demonstrated an impairment in one or more of eight areas of cognitive ability. In 70% of our patients with cognitive impairment, the dysfunction was classified as mild, implying that the impairment was established in only one or two cognitive domains. Eleven patients had three or more impaired areas, fulfilling the criteria for cognitive impairment used in other studies.[21] Based on this definition, only 24% of our study population would have been classified as having a cognitive impairment. This figure is in accordance with prevalence rates of 21% in a study of 70 unselected patients with SLE[21] and 26% in a study of 73 patients.[22]

In our study population, 25 patients (54%) had had headache, with lifetime prevalence of migraine and tension headache being 39 and 15%. The prevalence of tension headache in our study was actually slightly lower than in the healthy population.[27-29]

The reported prevalence rates of psychiatric manifestations in SLE have varied from 20 to 70%.[22,30] Recent reports have focused on the occurrence of milder psychiatric features such as depression and anxiety, whereas, in contrast to older studies, low prevalence of psychosis has been observed.[20,22] Our results corroborate this finding: 80% of patients with mood disorder had mild depression requiring no medication, whereas none had experienced any episode of psychosis.

Cerebrovascular disease was diagnosed in seven (15%) of our patients with SLE. In earlier studies, the frequency of stroke varied from 3 to 19%.[15-19,31] Patients with SLE who have had a stroke or transient ischemic attack are at high risk for recurrent cerebral ischemia.[32] Two of our seven patients with cerebrovascular disease had a recurrence of stroke or transient ischemic attack, and one had a chronic multifocal disease. A significantly higher cumulative lifetime dose of steroids in patients with SLE with a history of cerebrovascular disease obviously reflects the severity of this subgroup.

A mild, symmetric distal sensory or sensorimotor neuropathy is the most common form of peripheral neuropathies in SLE.[16] A 28% frequency of polyneuropathy in the current study is certainly overestimated, because the ACR nomenclature system does

not demand an ENMG confirmation of polyneuropathy. The corresponding prevalence of ENMG-confirmed polyneuropathy in our series was 7%, in accordance with the previous studies.[15-18,33-34]

One of the patients fulfilled the ACR nomenclature criteria for a demyelinating syndrome which may be reminiscent of MS.[35-36] Our patient had neurologic and MRI findings similar to MS, but a high positive titer of aCL together with the history of thrombocytopenia and deep venous thrombosis strongly favors the diagnosis of antiphospholipid syndrome. Oligoclonal banding has been described to occur in patients with secondary antiphospholipid syndrome caused by SLE.[36] We suggest that future revisions of the ACR nomenclature system specifically exclude antiphospholipid syndrome in the diagnosis of a demyelinating syndrome.

The main weakness of the study is the small sample size, and therefore the results should to be interpreted with caution. As a cross-sectional study, the validity of disease history depends on the documentation of past disease episodes. We think that this is unlikely to have a substantial effect on the prevalence rates of the NP syndromes, but reliable discrimination between primary NPSLE, secondary NPSLE, and concurrent disease process becomes problematic. It has been estimated that two-thirds of NP manifestations in SLE are not directly related to NPSLE but are due to secondary causes such as drugs, infections, and metabolic complications of the disease.[37,38] Prospective analyses would help in discriminating between primary and secondary NPSLE.

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Current management of ALS

Comparison of the ALS CARE Database and the AAN Practice Parameter

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Article abstract—*Background:* The American Academy of Neurology (AAN) ALS Practice Parameter was published in April 1999. The ALS CARE Database has been collecting data on the management of patients with ALS in North America since 1996. *Objective:* To compare the management of patients with ALS in North America as recorded in the ALS CARE Database with the recommendations of the AAN ALS Practice Parameter. *Methods:* Data were analyzed from 2018 patients at enrollment and from 373 of these patients who died between enrollment and May 1999. *Results:* Eighty-two percent of the enrolled patients reported that they had been given enough information about ALS. Only 54% of patients with drooling were receiving medication for this problem. Only 41% of those who reported being depressed most of the time were receiving antidepressant medications. Only 28% of those with dyspnea and only 9.2% of those with a forced vital capacity <40% predicted were receiving noninvasive positive pressure ventilator support. Only 30% of those with moderate to severe dysphagia had a gastrostomy tube. Half of the patients who died did so at home, but only 47% of them received residential hospice services. Although 89% of patients who died were recorded as having done so peacefully, 17% were reported to have had breathing difficulties (i.e., respiratory distress), 8% anxiety, 3.3% pain, and 2.5% choking. Advance directives were in place for 90% of the patients who died, and in 97% of cases these directives were followed. *Conclusions:* These findings indicate that in the 3-year period prior to the publication of the AAN Practice Parameter, many but not all patients received the care that is recommended in that parameter; there were deficiencies, particularly in the key areas of gastrostomy and noninvasive positive pressure ventilation.

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The ALS CARE Database has been collecting information on patients with ALS, their caregivers, and their management since July 1996.[1-4] Currently there are 91 clinical sites that have enrolled more than 2500 patients. The American Academy of Neurology (AAN) ALS Practice Parameter was published in the April 1999 issue of *Neurology*.[5] One of the goals of this practice parameter is to influence the clinical management of patients with ALS. To observe whether this goal has been achieved, it will be necessary to monitor the management of patients with ALS over time after the publication of the practice parameter. We report here a comparison of the recommendations of the AAN ALS Practice Parameter with the baseline features of the management of patients with ALS extracted from the ALS CARE Database for patients enrolled in the 3-year period before the publication of the practice parameter. Our long-term goal is to repeat this study after an interval of a few years to examine the effect of the publication and dissemination of the AAN ALS Practice Parameter.

We also intend to determine whether the current ALS CARE Database questionnaire provides suffi-

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*See the Appendix on page 504 for a complete list of the investigators in the ALS CARE Study Group.

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ORIGINAL ARTICLE

Validity of the New American College of Rheumatology Criteria for Neuropsychiatric Lupus Syndromes: A Population-Based Evaluation

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Objective. **To assess the validity of the recently developed American College of Rheumatology (ACR) nomenclature for neuropsychiatric systemic lupus erythematosus (NPSLE).**

Methods. **We conducted a cross-sectional, population-based study covering an area with 440,000 people. A total of 46 patients aged 16 to 65 years fulfilled the criteria for a definite diagnosis of SLE. One control for each patient matched by age, sex, education, and place of residence was randomly identified from the population register. All patients and controls underwent a clinical neurologic examination and neuropsychological testing. The data were analyzed using conditional logistic regression methods.**

Results. **Forty-two patients (91%) and 25 controls (56%) fulfilled at least one of the ACR NPSLE criteria, which gave an odds ratio (OR) of 9.5 (95% confidence interval [CI] 2.2–40.8) but low specificity (0.46). Cognitive dysfunction was the most common syndrome detected in 37 patients (80%). A revised set of 16 criteria excluding the syndromes without evidence for neuronal damage resulted in improved specificity (OR 7.0, 95% CI 2.1–23.5, specificity 0.93).**

Conclusion. **The proposed 19 ACR criteria did not differentiate SLE patients from controls, nor NPSLE patients from other SLE patients. The revised NPSLE criteria proposed by us performed well in our population but should be evaluated in a larger patient population.**

KEY WORDS. Systemic lupus erythematosus; Neuropsychiatric; Diagnosis; Classification; Criteria.

INTRODUCTION

Systemic lupus erythematosus (SLE) has frequent and potentially serious neuropsychiatric (NP) manifestations that are of importance in the management of the disease. Lack of a diagnostic gold standard and ambiguous terminology have hampered epidemiologic research in neuropsychiatric systemic lupus erythematosus (NPSLE). The reported prevalence of NPSLE varies widely, from 14% to 75%, because of inconsistent classifications and selected patient populations in tertiary referral centers (1,2). A nomenclature system recently developed by the American College of Rheumatology (ACR; formerly the American Rheumatism Association) is the first step toward standardized and internationally accepted classification of NPSLE (3). This nomenclature comprises case definitions including diagnostic criteria, exclusions, and methods of ascertainment for a total of 19 syndromes (3) (Table 1). The purpose of this cross-sectional, population-based study is to assess the validity of the ACR nomenclature and case definitions for NPSLE.

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PATIENTS AND METHODS

Patients. The study base was Pirkanmaa Health Care District, located in southern Finland, with a population of 440,000 in 1998. The majority of new SLE patients in the area are referred to Tampere University Hospital for diagnostic evaluation and therapeutic planning. In some cases, diagnosis and followup are done in a local rheumatologic outpatient clinic or in any of the 3 district hospitals. All SLE patients were identified from computerized discharge

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Table 1. The neuropsychiatric syndromes in systemis lupus erythematosus according to the American College of Rheumatology nomenclature and case definitions (3)

Central nervous system	Peripheral nervous system
Aseptic meningitis	Acute inflammatory demyelinating polyradiculo-neuropathy
Cerebrovascular disease	Autonomic disorder
Demyelinating syndrome	Mononeuropathy, single/multiplex
Headache	Myasthenia gravis
Movement disorder (chorea)	Neuropathy, cranial
Myelopathy	Plexopathy
Seizure disorders	Polyneuropathy
Acute confusional state	
Anxiety disorder	
Cognitive dysfunction	
Mood disorder	
Psychosis	

registers of Tampere University Hospital, the 3 district hospitals, and the local outpatient clinic. Medical records of all patients with the diagnosis of SLE between January 1980 and December 1997 were examined to select patients who 1) fulfilled 4 or more of the ACR revised criteria for the disease (4), 2) were alive in 1998, 3) were 16 to 65 years of age in 1998, 4) were of native Finnish origin, and 5) were resident in the study area. Exclusion criteria were other coexistent connective tissue diseases, such as rheumatoid arthritis, mixed connective tissue disease, Sjögren's syndrome, or progressive systemic sclerosis.

A total of 58 eligible patients were identified. They were contacted by mail, and 46 of them (79%) gave consent for participation. The control group consisted of 46 individuals randomly identified from the Finnish Population Register, with matching by age, sex, level of education, and municipality of residence. Similar eligibility criteria were applied as for the patients. All participants gave a written informed consent, and the study protocol was approved by the local Ethics Committee.

The study group consisted of 39 female and 7 male SLE patients, with a mean age of 45 ± 13 years (range 20–64), and a similar number of matched controls. The mean disease duration since diagnosis of SLE was 14 ± 8 years (range 2–37), and the mean number of ACR SLE criteria fulfilled was 5.5 ± 1.2 (median 5, range 4–9). The mean European Consensus Lupus Activity Measurement (ECLAM) score was 1.7 (range 0–4), indicating very mild disease activity. Patients and controls had completed 13 ± 2.7 (range 8–18) and 13 ± 3.4 (range 7–20) years of education, respectively.

Methods. All patients and controls gave a complete medical history and underwent a clinical neurologic examination, performed by the same neurologist (HA) between November 1998 and May 1999. Disease activity was quantified using the ECLAM (5). Accumulated NP abnormality was assessed by using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index (6).

The diagnoses of neuropsychiatric syndromes were based on both past medical history and current findings in clinical examination. All syndromes detected in these patients were classified according to the standardized ACR nomenclature and case definition system for NPSLE (3). In both SLE patients and controls with clinical signs or symptoms suggesting polyneuropathy, electroneuromyography (ENMG) was performed.

Neuropsychological measures. In accordance with the ACR case definitions, all patients and controls completed a battery of neuropsychological tests in order to detect possible impairment in one or more of the cognitive domains, including simple attention, complex attention, memory, visual-spatial processing, language, reasoning/problem-solving, psychomotor speed, and executive functions. The test battery included Wechsler Adult Intelligence Scale-Revised (WAIS-R; Information, Vocabulary, Digit Span, Comprehension, Picture Completion, Block Design, and Digit Symbol Substitution subtests); Wechsler Memory Scale-Revised (Logical Memory and Drawings 1 hour delayed); California Verbal Learning Test; Continuous Performance Test; Simple Reaction Time (right and left hand); Wisconsin Card Sorting Test (computerized version, WCST-CV2); Boston Naming Test; Verbal Fluency; Category Fluency; Trail Making A; Trail Making B; and Stroop. Tests were administered by a trained clinical psychologist (JL). An average of 3 to 4 hours was required to complete the tests.

The individual test results were converted into standard scores, which were compared with the available normative data (7–11). Subjects with a total score that was 2 or more standard deviations (SD) below the normative value in any of the 8 cognitive domains were considered impaired. Premorbid level of functioning was estimated by using the 2 best scores from WAIS-R, excluding the Digit Symbol Substitution and Digit Span subtests. Education and occupation of the subject were taken into consideration in assessment of individual test performance. The same method was used to determine the highest level of functioning in controls. Cognitive dysfunction was classified as mild if there were deficits in fewer than 3 dimensions, moderate if there were deficits in 3 or 4 dimensions, and severe if there were deficits in at least 5 dimensions.

Assessment of depression was based on clinical interview and the Beck Depression Inventory (BDI) (12,13). On the BDI, scores between 10 and 17 were considered as mild, scores between 18 and 24 as moderate, and scores

Table 2. Neuropsychiatric syndromes in SLE patients and controls

Neuropsychiatric syndrome	Patient n (%)	Control n (%)	OR (95% CI)
Cognitive dysfunction	37 (80)	13 (28)	9.0 (2.7–29.7)
Mild	26	11	
Moderate	7	2	
Severe	4	0	
Headache	25 (54)	11 (24)	3.0 (1.3–7.1)
Migraine without aura	6	4	
Migraine with aura	12	5	
Tension headache	7	2	
Mood disorders	20 (44)	4 (9)	9.0 (2.1–38.8)
Major depressive-like episode	18	4	
Mood disorder with mixed features	2	0	
Polyneuropathy	13 (28)	5 (11)	3.7 (1.0–13.1)
ENMG confirmation	3	0	
Cerebrovascular disease*	7 (15)	0	∞
Stroke syndrome	5		
Transient ischemic attack	2		
Chronic multifocal disease	1		
Anxiety disorder	6 (13)	3 (7)	2.0 (0.5–8.0)
Seizures	4 (9)	1 (2)	4.0 (0.5–35.8)
Acute confusional state	3 (7)	0	∞
Neuropathy, cranial†	3 (7)	0	∞
Aseptic meningitis	1 (2)	0	∞
Demyelinating syndrome	1	0	∞
Movement disorder	1	0	∞
Myasthenia gravis	1	0	∞

* One patient had both a stroke and a transient ischemic attack.
† Optic neuritis in all cases.
SLE = systemic lupus erythematosus; ENMG = electroneuromyography.

over 24 as severe depression. However, the final grading of depression was based on clinical interview by the psychologist. Anxiety was evaluated by the psychologist on clinical interview.

Statistical methods. The prevalence of each condition included in the ACR criteria was calculated for SLE cases and controls. The odds ratio (OR) was calculated as the ratio of discordant pairs with a positive patient to pairs with a positive control. The data were analyzed with conditional logistic regression methods, using presence or absence of SLE as the outcome measure and various diagnostic criteria as explanatory variables.

RESULTS

All syndromes included in the proposed ACR criteria for NPSLE were more frequent among SLE patients than controls (Table 2). However, most syndromes were also found among controls, which resulted in low specificity. At least one NP syndrome was identified in 42 SLE patients (91%) and 25 controls (54%). This corresponds to an OR of 9.5 (95% confidence interval [CI] 2.21–40.8) and yields a specificity of 0.46 (21/46) and a detection rate of 91% (42/46) among SLE patients (Table 3).

To improve the criteria we constructed revised criteria based on objective findings only (Table 4). We excluded entirely anxiety and headache, as well as mild depression, mild cognitive dysfunction (with deficits in fewer than 3 dimensions) and polyneuropathy unconfirmed by ENMG. With these modifications, the proportion of controls fulfilling at least 1 of the criteria was substantially lower (7% versus 54%). Also, the proportion of SLE patients with at least 1 objective criterion was half of that for the proposed ACR criteria (46% versus 91%). With a cut-point of 1 the OR for the revised criteria was 7.0 (95% CI 2.09–23.47), with a specificity of 0.93 (43/46) and detection rate among SLE cases of 46% (21/46).

No major differences in the validity of the revised criteria were observed when compared by age, sex, or disease duration. The revised criteria showed a slightly higher correlation with the neuropsychiatric SLICC damage index than the proposed ACR criteria ($r = 0.79$ and $r = 0.58$, respectively). Neither ACR nor our revised criteria were correlated with current disease activity, as measured with ECLAM ($r = 0.08$ for both).

DISCUSSION

In this population-based sample, the ACR criteria and case definitions for NPSLE had a low specificity (i.e., could not differentiate SLE patients from controls). Ideally, case definitions should be based on SLE activity in the nervous system manifested as neurologic dysfunction (14). In most previous studies the diagnosis of NPSLE was based entirely on the presence of major neurologic and psychiatric impairment, including cerebrovascular event, neuropathy, movement disorder, transverse myelitis, seizure, meningi-

Table 3. Number of American College of Rheumatology (ACR) criteria and revised criteria for neuropsychiatric SLE among patient and control groups

	Patients	Controls	OR (95% CI)	Specificity
ACR criteria				
> 0	42	25	9.5 (2.2–40.8)	0.46
> 1	37	10	7.8 (2.7–22.0)	0.78
> 2	25	2	24.0 (3.3–177.4)	0.96
> 3	10	—	∞	1.00
Revised criteria				
> 0	21	3	7.0 (2.1–23.5)	0.93
> 1	9	0	∞	1.00
> 2	6	0	∞	1.00
> 3	2	0	∞	1.00

SLE = systemic lupus erythematosus.

tis, organic brain syndrome, and psychosis. No underlying neurologic injury, however, has been demonstrated for several syndromes listed under case definitions in the current ACR nomenclature for NPSLE. We propose a more stringent set of criteria based solely on manifestations of neurologic injury.

Signs of minor CNS dysfunction were frequent among both SLE patients and controls, which led to poor specificity and lack of distinction between the 2 groups. For example, it is very difficult to justify the inclusion of headaches: Although they were more common among patients than controls (54% versus 24%), the high prevalence among controls did not allow distinction between NPSLE and other conditions manifesting as headache. In a recent report, headaches were not associated with disease activity (15). Tension-type headache in SLE patients was associated with psychological distress and depressive mood, while migraine was associated only with a tendency to social isolation and anxiety. These findings indicate that headaches are not a NP manifestation in SLE. Furthermore, ACR case definitions do not include ENMG for diagnosing polyneuropathy. Our results, with more than 10% of controls presenting with sensory or motor symptoms, indicate that subjective symptoms are too vague and unspecific, and ENMG confirmation is required to demonstrate neurologic injury.

Despite its frequency among SLE cases, mild cognitive dysfunction was not specific for NPSLE, because it was also detected among one fourth of controls. According to ACR case definitions, documented impairment in one of the cognitive domains is sufficient for the diagnosis of cognitive dysfunction. Previously, it has been proposed that a minimum of 3 impaired domains is required (16). Our results indicate that this is required for detecting clinically relevant neuropsychological defect.

Mild depression and anxiety are common in otherwise healthy subjects and even more so among patients with chronic diseases (17,18). They can be regarded as psychological responses to illness and therefore not specific for NPSLE (19). Functional brain imaging techniques have demonstrated that major depression is associated with both reversible and irreversible neurophysiological abnormalities in some structures (20). Major depression can be considered analogous to psychosis in psychiatric morbidity, and its inclusion in the diagnostic criteria for NPSLE is probably justified.

Our results demonstrate inadequate performance of the proposed ACR criteria. It appears that NPSLE has no pathognomonic manifestations but does share features with other CNS conditions. Therefore, revised criteria are needed to distinguish NPSLE from other conditions. We derived criteria based on neurologic injury and excluded conditions that do not indicate a neurologic dysfunction. A higher correlation with SLICC for our revised criteria

Table 4. The modified criteria for neuropsychiatric systemic lupus erythematosus

Central nervous system	Peripheral nervous system
Aseptic meningitis	Acute inflammatory demyelinating polyradiculo-neuropathy
Cerebrovascular disease	Autonomic disorder
Demyelinating syndrome	Mononeuropathy, single/multiplex
Movement disorder (chorea)	Myasthenia gravis
Myelopathy	Neuropathy, cranial
Seizure disorders	Plexopathy
Acute confusional state	Polyneuropathy (with ENMG* confirmation)
Cognitive dysfunction (moderate or severe)	
Severe depression	
Psychosis	

* ENMG = electroneuromyography.

than for ACR criteria lends further credence to our approach. To support our basis of classification, further research on organic nervous system damage with pathogenetic mechanisms specific to SLE is warranted.

We were able to define a study base and identify all prevalent cases of SLE and population-based controls in it. Matching for age, sex, and education was used to maximize comparability between patients and controls, as well as to minimize loss of information. In principle, there are 2 possible designs for evaluating diagnostic criteria. First, a direct approach would encompass assessment of patients suspected of having the target condition (i.e., representing a true clinical context and comparing the test being evaluated with a gold standard). Yet this is not feasible for NPSLE because of the lack of accessible defining criteria for NPSLE (i.e., a gold standard). Therefore, the only way to evaluate the criteria is by comparing patients with the disease and a sample of subjects without it. Because no definite method for identifying patients with NPSLE is available, we compared the prevalence of symptoms proposed as criteria and case definitions for NPSLE between SLE patients (instead of NPSLE patients) and controls. In other words, we used SLE as a proxy for NPSLE. This is logical because, by definition, NPSLE can occur only among patients with SLE. However, SLE is a necessary but not sufficient condition for NPSLE; that is, it is a sensitive but not specific definition. It has been shown that this leads to some loss of statistical power but does not bias the results (21). Even though the proposed ACR criteria are designed for use among SLE patients, evaluation of their sensitivity and specificity is not possible without a control group free of SLE.

Small sample size limited the statistical power of the analyses; therefore, rare syndromes as manifestations of NPSLE could not be assessed in our material. Further studies with larger patient populations are likely to reveal more subtle differences between SLE patients and controls.

The diagnostic criteria for NPSLE proposed by ACR appear to have specificity that is too low and a detection rate that is unrealistically high to be clinically useful.

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Increased Serum Matrix Metalloproteinase 9 Levels in Systemic Lupus Erythematosus Patients With Neuropsychiatric Manifestations and Brain Magnetic Resonance Imaging Abnormalities

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Objective. **To evaluate whether serum matrix metalloproteinase 9 (MMP-9) levels are associated with neuropsychiatric manifestations, particularly cognitive dysfunction, as evaluated by neuropsychological testing and brain magnetic resonance imaging (MRI) abnormalities in patients with systemic lupus erythematosus (SLE).**

Methods. **MMP-9 determinations were made in 44 patients with SLE and 43 healthy controls who underwent a clinical neurologic and neuropsychological investigation in order to identify neuropsychiatric manifestations. Cerebral MRI scans with volumetric estimation of intracranial cerebrospinal fluid spaces, T1-weighted lesions, and T2-weighted lesions were performed for all subjects. SLE activity was assessed by the European Consensus Lupus Activity Measure (ECLAM) index, and accumulated neuropsychiatric abnormality was assessed by the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology damage index.**

Results. **No significant difference was found in serum MMP-9 levels between the overall group of SLE patients and controls. However, SLE patients who had at least 1 neuropsychiatric manifestation (NPSLE patients) had significantly higher serum MMP-9 concentrations than did SLE patients without neuropsychiatric syndromes ($P = 0.009$). Among patients with NPSLE, those with cognitive deficits had significantly higher concentrations of serum MMP-9 than did those with normal cognitive function ($P = 0.027$). Furthermore, serum MMP-9 levels had a significant positive correlation with the volumes of T1-weighted and T2-weighted lesions in the brain MRI ($P = 0.031$ and $P = 0.015$, respectively). The concentration of serum MMP-9 correlated significantly with the SLICC index but not with the ECLAM index.**

Conclusion. **Elevated levels of serum MMP-9 in patients with SLE may reflect neuropsychiatric involvement, particularly cognitive dysfunction. The serum MMP-9 concentration may be associated with small-vessel cerebral vasculopathy and increased risk of cerebral ischemic events in patients with SLE.**

Neuropsychiatric manifestations of systemic lupus erythematosus (SLE) are common and may affect up to two-thirds of patients with this disease. According to the definition of neuropsychiatric SLE (NPSLE), this condition includes neurologic syndromes of the central, peripheral, and autonomic nervous system and the psychiatric syndromes observed in patients with SLE for which other causes have been excluded (1). The pathogenesis of NPSLE is still unclear, but recent studies on neuroimaging have greatly advanced the understanding of this disease, which appears to be caused by both acute and chronic brain injury induced by the complex pathologic processes of SLE (2). An important cause of the central nervous system (CNS) syndromes in SLE is

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ischemia due to narrowing or occlusion of small vessels (3). The most commonly observed cerebral magnetic resonance imaging (MRI) abnormalities include cortical stroke, global atrophy, and nonspecific foci of increased signal in both gray and white matter, even though no consistent pattern of abnormality is characteristic of NPSLE (4). In general, the diagnosis of NPSLE is difficult, because no single laboratory marker or imaging modality serves as a gold standard, and the diagnosis is primarily clinical (5).

Matrix metalloproteinases (MMPs) are a family of zinc-containing endoproteinases that can degrade a variety of extracellular matrix components (6). MMP-9 is a gelatinase that is secreted by several cell types of the vessel wall, including macrophages, T lymphocytes, endothelial cells, and smooth muscle cells (7). Macrophage-produced MMP-9 has been shown to play a role in the pathogenesis of atherosclerosis by weakening the arterial wall; this process can result in plaque rupture and thereby in thrombus formation and occlusion of the artery (8). The principal function of MMP-9 produced by T cells is to enhance T cell migration through connective tissue (9). Increased activity of MMPs has been implicated in numerous disease processes, including malignancies, cardiovascular diseases, and autoimmune diseases such as multiple sclerosis, Guillain-Barré syndrome, and rheumatoid arthritis (10–16). To date, serum MMP-9 levels in SLE have been investigated in only one study, the results of which showed that MMP-9 activity is significantly elevated in patients compared with controls (17).

The aim of this study was to evaluate and test the hypothesis that serum MMP-9 levels are associated with neuropsychiatric manifestations or cerebral MRI abnormalities in patients with SLE.

PATIENTS AND METHODS

Patient selection. The study group comprised 39 women and 7 men with SLE (mean ± SD age 45 ± 13 years [range 20–64 years]) and a similar number of matched controls. The total patient sample was the same as that described in our previous report (18). The study base was Pirkanmaa Health Care District, located in southern Finland, with a population of 440,000. We identified patients with SLE by using the computerized databases of Tampere University Hospital, the 3 district hospitals, and a local outpatient clinic. Medical records of both inpatients and outpatients coded for the diagnosis of SLE between January 1980 and December 1997 were examined to select patients who fulfilled ≥4 of the 1982 revised American College of Rheumatology (ACR) criteria for the disease (19), were ages 16–65 years and of native Finnish origin, and resided in the study area. Patients with other connective tissue diseases were excluded.

Table 1. Neuropsychiatric syndromes in 46 patients with SLE*

Neuropsychiatric syndrome	No. (%)
Cognitive dysfunction	11 (24)
Cerebrovascular disease	7 (15)
Seizure disorder	4 (9)
Acute confusional state	3 (7)
Neuropathy, cranial	3 (7)
Polyneuropathy	3 (7)
Aseptic meningitis	1 (2)
Demyelinating syndrome	1 (2)
Movement disorder (chorea)	1 (2)
Myasthenia gravis	1 (2)

* Nine patients had >1 neuropsychiatric manifestation. SLE = systemic lupus erythematosus.

We identified 110 patients with SLE. Of these, 15 patients had died, and 37 did not meet the inclusion criteria. The remaining 58 patients were contacted by mail, and 46 of them (79%) agreed to participate in the study. The mean ± SD time since diagnosis of SLE was 14 ± 8 years (range 2–37 years), and the median number of ACR SLE criteria fulfilled was 5 (range 4–9). The control group consisted of 46 individuals randomly identified from the Finnish Population Register, who were matched with patients for age, sex, level of education, and municipality of residence. Eligibility criteria similar to those for the patients were applied. All participants gave written informed consent, and the study protocol was approved by the local ethics committee.

Clinical evaluation. The diagnosis of various neuropsychiatric syndromes was based on the clinical impression of one evaluator (HA) following review of the medical history, clinical examination, review of medical records, and neuropsychological testing. All past and present neuropsychiatric syndromes were listed and classified according to the modified ACR nomenclature and case definitions (20) (Table 1). If one of the neuropsychiatric syndromes was identified in a patient, he or she was considered to have NPSLE. NPSLE was identified in 21 (46%) of the 46 patients.

All patients and controls completed a 3-hour battery of neuropsychological tests administered by the same psychologist; details regarding the procedure and analysis of neuropsychological measures have been described elsewhere (18). The number of the ACR revised diagnostic criteria for SLE, and current and previous use of steroids and other immunosuppressive medication were recorded. A cumulative lifetime dose of steroids (expressed as grams of prednisolone) was determined from the patient records. Individual disease activity was quantified using the European Consensus Lupus Activity Measurement (ECLAM) scale (21). Accumulated neuropsychiatric abnormality was assessed using the Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage index (22). Neuropsychiatric manifestations of the damage index that were scored included cognitive impairment, major psychosis, seizures requiring therapy for 6 months, cerebral vascular accident, cranial or peripheral neuropathy (excluding optic), and transverse myelitis.

Table 2. Baseline characteristics and laboratory values in 46 SLE patients and 46 controls*

Characteristic	SLE patients	Controls	*P*
Age, years	45 ± 12.6	45 ± 12.7	–
No. men/no. women	7/39	7/39	–
Disease duration, years	14.2 ± 8.0	–	–
Education completed, years	13 ± 2.7	13 ± 3.4	–
Serum MMP-9, μg/liter†	56.7 ± 39.4	58.8 ± 23.8	0.13
B leukocytes, 10^9/liter	5.7 ± 2.7	6.0 ± 1.5	0.20
B hemoglobin, gm/liter	131.0 ± 14.0	134.2 ± 11.2	0.28
B thrombocytes, 10^9/liter	253.4 ± 135.3	250.0 ± 51.9	0.38
Serum C3, gm/liter	0.90 ± 0.31	1.04 ± 0.20	0.008
Serum C4, gm/liter	0.14 ± 0.09	0.22 ± 0.06	<0.001
Serum CH50, units/ml	53.5 ± 24.3	70.3 ± 17.4	<0.001
ESR, mm/hour	23.2 ± 16.3	9.0 ± 6.3	<0.001
Anti-dsDNA antibodies, units/liter	159.4 ± 238.0	40.2 ± 1.8	<0.001
Antinuclear antibodies, titer	1,258.3 ± 1042.4	90.4 ± 49.5	<0.001
Anticardiolipin antibodies, GPL units	12.9 ± 24.5	2.3 ± 8.42	<0.001

* Except where indicated otherwise, values are the mean ± SD. SLE = systemic lupus erythematosus; MMP-9 = matrix metalloproteinase 9; ESR = erythrocyte sedimentation rate; anti-dsDNA = anti–double-stranded DNA; GPL = IgG phospholipid. *P* values were determined by Mann-Whitney U test.
† Determined in 44 patients and 43 controls.

Laboratory evaluation. Quantitation of immunoreactive MMP-9 was carried out by enzyme-linked immunosorbent assay (ELISA; Diabor, Oulu, Finland). ELISAs were performed on 96-well microtiter plates using standard protocols. Recombinant MMP-9 was used as a standard. The microtiter plate was coated with the monoclonal antibody (code GE-213), and samples and standards were added. The bound proteins were detected with a secondary polyclonal antibody produced in chicken against MMP-9. Peroxidase-labeled anti-chicken IgG (Chemicon, Temecula, CA) was used for detection of the bound secondary antibody, and *o*-phenylenediamine tablets (KemEnTec, Copenhagen, Denmark) were used to visualize the peroxidase label. The color formation was measured at 450 nm on an Anthos 2000 microplate reader (Anthos Labtec Instruments, Frederick, MD), and calculations were done using a Multicalc program (Wallac, Turku, Finland). The monoclonal antibody recognizes both free MMP-9 and that bound to its inhibitor, tissue inhibitor of metalloproteinases 1 (23). Determination of the MMP-9 level was carried out concurrently with the clinical and neuropsychological evaluation. In 2 patients and 3 controls, determination of the MMP-9 level was not successful.

Other serologic tests included a complete blood cell count, erythrocyte sedimentation rate, serum creatinine concentration, and serum complement levels (CH50 and components C3 and C4). Antinuclear antibodies (ANAs), anti–double-stranded DNA (anti-dsDNA) antibodies, IgG type anticardiolipin antibodies (aCL), and β_2-glycoprotein I (β_2GPI) antibodies were measured by ELISA.

Neuroradiologic examinations. Cerebral MRI was performed on 43 SLE patients and 44 healthy controls. The Signa Easy Vision 1.5T MRI imaging system (General Electric Medical Systems, Milwaukee, WI) was used for all examinations. All MRI scans were read in a blinded manner by an experienced neuroradiologist (PD) who did not have access to any demographic or clinical data. MRI scans in patients and controls were performed a mean ± SD of 11.1 ± 11.6 weeks and 17.1 ± 7.6 weeks, respectively, after the clinical evaluation was performed and blood was drawn. The MRI protocol included sagittal T1-weighted, axial T1-weighted, axial T2-weighted, and coronal fluid-attenuated inversion recovery (FLAIR) sequences. The imaging protocol also included axial 3-dimensional (3-D) T2 fast spin-echo and gadolinium-diethylenetriaminepentaacetic acid–enhanced 3-D T1 spoiled gradient-echo images for segmentation and volumetric analysis. Segmentation and volumetric analysis were performed using the segmentation software Anatomatic, operating in PC/Windows 95 environment (24–26). Segmentation and volumetric measurements of hypointense lesions on T1-weighted images and hyperintense lesions on T2-weighted images were performed separately.

T1-weighted images showed only gliotic infarcts, and T2-weighted images showed also microinfarcts, ischemic lesions, and demyelinating lesions. Any small T2-weighted hyperintense lesions that looked like age-related changes were excluded. The criteria for age-related changes were as follows: small periventricular T2 high-signal-intensity changes in the area of frontal and occipital horns, few scattered well-defined small-size (<3 mm) T2 high-signal-intensity changes in the area of centrum semiovale that are not visible on T1-weighted images, and widened Virchow-Robin spaces that are seen as low-signal-intensity areas on FLAIR images. Measurements were expressed as volume/cm^3.

The markers for cerebral atrophy were intracranial cerebrospinal fluid (CSF) space volume and relative intracranial CSF space volume. Volumetric measurement of total intracranial CSF spaces was done by assessing the total volume of the ventricular and peripheral CSF spaces, expressed as volume/cm^3. Total intracranial volume was measured by calculating together the volume of all the segmented gray and white matter and intracranial CSF spaces. Relative intracranial CSF space volume was defined as volumetric measurement of relative intracranial CSF space, and was determined by dividing the total intracranial CSF space volume by the total brain volume.

Statistical analysis. All statistical analyses were performed on a microcomputer using SPSS software (version 11.0, 2002; SPSS, Chicago, IL). The significance of differences in the levels of serum MMP-9 between study groups was determined using the Mann-Whitney U test or nonparametric analysis of

Table 3. Correlations between serum MMP-9 levels and laboratory test results in 44 patients with SLE and 43 controls*

Laboratory parameter	Patients		Controls	
	r	*P*	r	*P*
B leukocytes	0.68	<0.001	0.55	<0.0001
Serum C4	0.42	0.005	0.28	0.07
B thrombocytes	0.40	0.007	0.10	0.54
B hemoglobin	0.33	0.03	0.34	0.02
Serum C3	0.30	0.05	0.09	0.57
Serum CH50	0.28	0.07	0.22	0.16
Anticardiolipin antibodies	−0.04	0.79	0.13	0.41
β_2-glycoprotein I antibodies	0.22	0.32	–	–
Anti-dsDNA	−0.34	0.02	−0.19	0.23
ESR	−0.04	0.81	−0.002	0.10
Antinuclear antibodies	−0.43	0.003	−0.23	0.14

* *P* values were determined by Spearman's rank order correlation test. See Table 2 for definitions.

variance (ANOVA). The correlation between MRI parameters and serum MMP-9 levels was analyzed using Spearman's rank correlation. Differences in the levels of serum MMP-9 between the ECLAM and SLICC/ACR groups were tested by ANOVA. *P* values less than 0.05 were considered significant.

RESULTS

Serum levels of MMP-9 and serologic indicators of disease activity in SLE patients and controls. The mean ± SD level of MMP-9 was 56.7 ± 39.4 μg/liter in SLE patients and 58.8 ± 23.8 μg/liter in controls ($P = 0.13$). A comparison of all laboratory parameters between SLE patients and controls is presented in Table 2. Correlations between serologic indicators of disease activity and MMP-9 levels in SLE patients and controls are shown in Table 3. A highly significant positive correlation was observed between serum MMP-9 levels and leukocytes in both patients and controls ($P < 0.0001$ for both), and a significant negative correlation was observed between serum MMP-9 levels and levels of anti-dsDNA and ANA in SLE patients. No significant correlation of serum MMP-9 with aCL or β_2GPI antibodies was detected.

Neuropsychiatric manifestations and serum levels of MMP-9. The relationship between concentrations of serum MMP-9 and neuropsychiatric manifestations in 44 patients with SLE was investigated (Table 4). NPSLE was diagnosed in 20 patients (45%), and the mean ± SD serum MMP-9 level in this group was 73.2 ± 46.1 μg/liter. In the remaining 24 patients without NPSLE, the mean ± SD MMP-9 level was 42.8 ± 26.8 μg/liter; the difference between mean values was statistically significant ($P = 0.009$) (Figure 1). When serum MMP-9 concentrations were evaluated with respect to different neuropsychiatric manifestations, the levels were significantly higher in patients in whom cognitive impairment was diagnosed (80.8 ± 45.8 μg/liter) than in those with normal cognitive function (48.6 ± 34.2 μg/liter; $P = 0.027$). In other neuropsychiatric syndromes, no statistically significantly higher or lower concentrations of MMP-9 were identified (Table 4). In SLE patients with polyneuropathy, the mean ± SD serum levels of MMP-9 were twice as high as those in patients without polyneuropathy (106.2 ± 56.3 μg/liter versus 53.0 ± 36.3 μg/liter), but, probably because of the small number of patients, the difference did not reach statistical signifi-

Table 4. Comparison of serum MMP-9 levels (μg/liter) in 44 SLE patients, by presence or absence of specific neuropsychiatric manifestations*

Manifestation	Neuropsychiatric manifestations		No neuropsychiatric manifestations		
	No. of patients	MMP-9 level	No. of patients	MMP-9 level	*P*
Cognitive dysfunction	11	80.8 ± 45.8	33	48.6 ± 34.2	0.027
Cerebrovascular disease	7	76.3 ± 43.9	37	53.0 ± 38.1	0.092
Seizure disorder	4	82.9 ± 50.1	40	54.0 ± 38.0	0.111
Severe depression	4	27.9 ± 12.2	40	59.5 ± 40.1	0.072
Polyneuropathy	3	106.2 ± 56.3	41	53.0 ± 36.3	0.081
Acute confusional state	3	62.4 ± 26.0	41	56.2 ± 40.4	0.442
Neuropathy, cranial	2	43.9 ± 45.6	42	57.3 ± 39.6	0.652
Aseptic meningitis	1	11.6	43	57.7 ± 39.3	0.106
Demyelinating syndrome	1	137.8	43	54.8 ± 37.8	0.125
Movement disorder	1	79.2	43	56.1 ± 39.7	0.288
Myasthenia gravis	1	64.1	43	56.5 ± 39.9	0.503

* Values are the mean ± SD. *P* values were determined by nonparametric analysis of variance. See Table 2 for definitions.

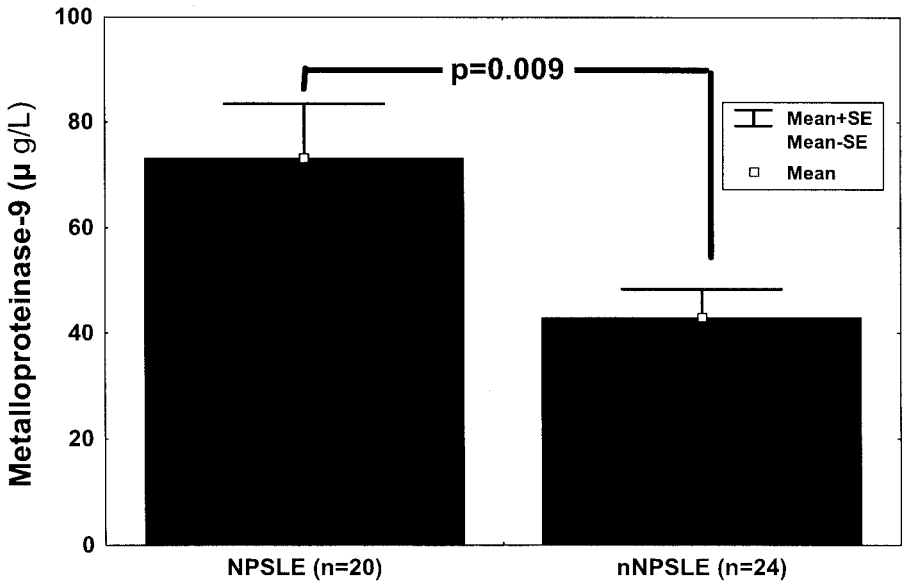

Figure 1. Serum matrix metalloproteinase 9 concentrations in patients with neuropsychiatric systemic lupus erythematosus (NPSLE) and in patients without NPSLE (nNPSLE). Statistical significance between the groups was determined by Mann-Whitney U test.

cance ($P = 0.081$). Similarly, in the 1 SLE patient with a demyelinating syndrome, the serum concentration of MMP-9 was almost 3-fold higher than the mean ± SD concentration in the 43 patients without a demyelinating syndrome (137.8 μg/liter versus 54.8 ± 37.8 μg/liter; $P = 0.125$). There was no statistically significant difference in the cumulative lifetime dose of glucocorticoids between SLE patients with and those without cognitive dysfunction.

Lupus disease activity/neuropsychiatric damage index and serum levels of MMP-9. Regression analysis to examine associations between levels of serum MMP-9 and SLE disease activity and neuropsychiatric damage indexes was performed. The mean ECLAM score was 1.6 (range 0–5), indicating very low disease activity. ANOVA revealed no significant relationship between individual MMP-9 levels and ECLAM scores. The mean (±SD) neuropsychiatric SLICC damage index score was also low (0.57 ± 1.00 [range 0–4]), with 32 patients having a score of 0, 6 patients having a score of 1, 5 patients having a score of 2, 2 patients having a score of 3, and 1 patient having a score of 4. Serum MMP-9 concentrations tended to be higher in patients with higher neuropsychiatric SLICC damage index scores, except in the 1 patient who had a score of 4. The result across these neuropsychiatric SLICC damage index score groups was statistically significant by ANOVA ($P = 0.048$). Serum MMP-9 levels did not correlate with disease duration ($r = 0.18$, $P = 0.25$). The mean level of serum MMP-9 was 65.7 μg/liter in patients with a history of nephritis and 50.4 μg/liter in patients without such a history; this difference did not reach statistical significance ($P = 0.21$). Similarly, no significant correlation between serum MMP-9 and creatinine levels was observed in SLE patients ($r = 0.27$, $P = 0.075$).

Treatment status and serum levels of MMP-9. The relationship between serum MMP-9 activity and treatment modalities in patients with SLE was investigated. At the time of the study, 25 patients were receiving glucocorticoids, 7 were being treated with antimalarial agents, 5 were receiving azathioprine, 2 were receiving methotrexate, and 1 patient was receiving cyclosporine. Eleven patients were receiving both glucocorticoids and cytotoxic drugs. A total of 19 patients (41%) were not receiving specific medication. No significant differences in serum levels of MMP-9 were found between the patients receiving either glucocorticoids or other immunomodulatory treatment and those who were not receiving any immunosuppressive treatment. Similarly, no significant correlation was observed between cumulative lifetime dose of glucocorticoids and serum MMP-9 levels ($r = 0.25$, $P = 0.12$).

MRI parameters and levels of serum MMP-9. Using Anatomatic segmentation software, it was esti-

Table 5. Correlation of MMP-9 values with quantitative MRI volumes in SLE patients*

MRI parameter	r	P*
T1-weighted volume, cm^3	0.33	0.031
T2-weighted volume, cm^3	0.371	0.015
Total intracranial CSF space volume, cm^3	−0.004	0.982
Relative intracranial CSF space volume	0.092	0.564

* MMP-9 = matrix metalloproteinase 9; MRI = magnetic resonance imaging; SLE = systemic lupus erythematosus; CSF = cerebrospinal fluid. Statistical values were determined by Spearman's rank correlation test.

mated that the mean ± SD volume of T1 lesions was 0.47 ± 1.42 volume/cm^3 in SLE patients versus 0.08 ± 0.30 volume/cm^3 in controls ($P = 0.0085$), and the mean ± SD volume of T2 lesions was 1.30 ± 0.68 volume/cm^3 versus 0.30 ± 0.11 volume/cm^3, respectively ($P < 0.001$). In the assessment of brain atrophy it was found that the mean intracranial CSF space volume in patients was 129.1 ± 39.9 volume/cm^3, compared with 83.6 ± 18.3 volume/cm^3 in controls ($P < 0.001$). The mean ± SD relative intracranial CSF space volume was 0.19 ± 0.07 in patients versus 0.11 ± 0.01 in controls ($P < 0.001$). In SLE patients, a positive significant correlation was observed both between the levels of serum MMP-9 and T1 lesions (r = 0.33, $P = 0.031$) and between the levels of serum MMP-9 and T2 lesions (r = 0.37, $P = 0.015$). No association was detected between the levels of serum MMP-9 and intracranial CSF space volume or relative intracranial CSF space volume. (Table 5). The cumulative lifetime dose of glucocorticoids showed a positive correlation with intracranial CSF space volume (r = 0.35, $P = 0.028$) and relative intracranial CSF space volume (r = 0.36, $P = 0.023$), but not with T1 and T2 lesions in SLE patients. In healthy controls, no correlations between the levels of serum MMP-9 and MRI parameters were observed.

DISCUSSION

We analyzed the concentrations of serum MMP-9 in 44 patients with SLE and 43 healthy controls and found no significant differences between the 2 groups. Our findings are not consistent with those from a previous study, which showed a significant increase of MMP-9 activity in the sera of 40 SLE patients compared with 25 healthy controls (17). Among other MMPs that have been studied, MMP-3 levels have been found to be elevated in SLE patients, and specifically in those with lupus nephritis (27,28). An increase in MMP-1 and MMP-2 activity has not been demonstrated in SLE (27).

In our study, patients with NPSLE had significantly higher levels of serum MMP-9 than did SLE patients without neuropsychiatric disease. In addition, a positive correlation of serum MMP-9 levels with the neuropsychiatric SLICC index score was detected. These 2 observations corroborate our primary hypothesis, according to which MMP-9 levels may reflect CNS injury in patients with SLE.

There has been speculation regarding whether or not metalloproteinases are related to disease activity in SLE. In a previous study, a positive correlation between the MMP-9 concentration and disease activity scores was observed, but only in men (17). In our study, no association between MMP-9 levels and ECLAM scores was found in either sex. This may be partly explained by the fact that at the time of the assessment, the majority of our patients were in good health (only 1 patient was hospitalized); as a consequence, the ECLAM scores in general were not high. In fact, if levels of MMP-9 truly parallel disease activity, these levels would be expected to be low in our patients.

Cognitive deficits occur in 21–81% of patients with SLE, depending on the criteria used and patient selection (18,29–34). In our study, based on a 3-hour battery of neuropsychological tests, cognitive deficits were diagnosed in 24% of the patients with SLE. Cognitive abnormalities in SLE may not be cumulative over time but may follow an evanescent course due to irreversible and, in part, reversible ischemic changes in the brain (3,35). Cerebral small-vessel vasculopathy (i.e., ischemia due to the narrowing or occlusion of small vessels, arteries, and veins) has been suggested to underlie the cognitive disorder in SLE (3). In our patients, serum MMP-9 levels were associated with T1 and T2 hyperintensities, which are major MRI indices of cerebral infarcts and may be derived from atherosclerosis in cerebral or carotid vessels (embolic infarcts). Moreover, our patients with cognitive deficits had higher serum concentrations of MMP-9 than did the SLE patients with normal cognitive function. These findings tempt us to speculate that the MMP-9 concentration relates to the underlying pathologic process, small-vessel vasculopathy. In our study, the elevated MMP-9 levels in SLE patients with cognitive dysfunction may reflect an ongoing, active process, because elevated plasma MMP-9 concentrations after acute coronary syndromes and successful reperfusion of acute myocardial infarction are reversible and gradually decrease to the levels observed in normal control subjects (11,36,37). This may also

explain why serum MMP-9 levels in SLE patients with a history of stroke were not high.

In previous studies of primary arteritis, macrophages within the inflamed artery wall showed increased expression of MMP-9, which was reflected also as increased serum levels of the enzyme (38). MMP-9 is a proteolytic enzyme that can degrade a variety of extracellular matrix components. By cleaving type IV collagen of the basement membrane and other extracellular matrix proteins, MMP-9 may favor leukocyte migration into the artery wall (6,9). In addition, MMP-9 expression is related to blood–brain barrier disruption after cerebral ischemia (39).

In MRI, T1-weighted hypointensities include primarily gliotic infarcts, but also (to a lesser extent) gliotic demyelinating plaques, which were not seen in our study. T2-weighted images are more sensitive in detecting microinfarcts and other ischemic lesions in spite of possible superimposed abnormalities (4). Previous findings have shown that ischemia is the main cause of CNS manifestations in SLE, and cerebral small-vessel angiopathy is the predominant histopathologic abnormality (3). Typical abnormalities on brain MRI are small punctate lesions of increased signal intensity, localized mainly in the periventricular and subcortical white matter, known also as white matter hyperintensities. The pathogenesis of these small infarcts in the brain is not clear (3). Our finding of the association between leukocyte count and serum MMP-9 concentration in both SLE patients and healthy controls confirms previous reports by Kalela et al (40) and supports the concept of MMP-9 being a useful marker of inflammation. Furthermore, our findings may indicate that there is an inflammatory process behind these small angiopathic changes in the brains of patients with SLE.

This study is the first to investigate the correlation between MMP-9 concentrations and MRI abnormalities in SLE, but the results are in accordance with those of earlier studies of MMP-9 levels, which showed increased MMP activity in patients with stroke and vascular dementia (i.e., clinical states associated with vasculopathy) (41,42). Consistent with our findings in SLE patients, a significant positive correlation between high serum levels of MMP-9 and the number of T1-weighted gadolinium-enhancing MRI lesions in patients with multiple sclerosis has been reported (12). The findings of increased CSF and serum levels of MMP-9 in patients with multiple sclerosis and expression of MMP-9 in demyelinating lesions have suggested that metalloproteinases may have importance in the pathogenesis of this disease (12–14). MMP-9 has also been related to other autoimmune disorders such as Guillain-Barré syndrome and experimental autoimmune neuritis (15,43). In relation to these diseases, it has been assumed that MMP-9 participates in the degradation of myelin basic protein, a major component of both CNS and peripheral nervous system myelin (15). Interestingly, demyelinating syndrome, which may clinically resemble multiple sclerosis, is listed as one of the manifestations of NPSLE. In our study, 1 patient was diagnosed as having demyelinating syndrome, and she had a high level of MMP-9 activity.

This is the first study in which MMP-9 concentrations in patients with NPSLE were evaluated. According to the results, elevated levels of serum MMP-9 in patients with SLE are associated with neuropsychiatric involvement, and cognitive dysfunction in particular. The findings further suggest a relationship between MMP-9 levels and ischemic changes on cerebral MRI, thus supporting the hypothesis that cerebral small-vessel vasculopathy may underlie the cognitive decline in SLE.

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Cerebral MRI abnormalities and their association with neuropsychiatric manifestations in SLE: a population-based study

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Objective: To evaluate the volumetric brain magnetic resonance imaging (MRI) findings in a population-based sample of systemic lupus erythematosus (SLE) patients and to detect a possible relationship between cerebral MRI abnormalities and specific neuropsychiatric (NP) manifestations.

Methods: The study population consisted of patients with SLE (n=43) in Pirkanmaa Health Care District, Finland and of a sex- and age-stratified reference group from the general population (n=43). In addition to a clinical neurological investigation, all subjects received a detailed neuropsychological assessment and an MRI study. Volumetric measures of cerebral atrophy as well as T1- and T2-weighted lesions were obtained. SLE activity was assessed by the European Consensus Lupus Activity Measure (ECLAM) index, and accumulated NP abnormalities were measured by the Systemic Lupus International Collaborating Clinics (SLICC) damage index. A cumulative lifetime dose of glucocorticoids was determined from the patient records.

Results: Compared with controls, SLE patients had increased volumes of both T1- and T2-weighted lesions ($p=0.019$ and $p<0.0001$, respectively) and increased cerebral atrophy ($p<0.001$). All the measured MRI parameters were statistically significantly higher in NPSLE than in non-NPSLE patients. In SLE patients, cerebral atrophy was associated with cognitive dysfunction, epileptic seizures, and cerebrovascular disease; T1-weighted lesions were associated with epileptic seizures and T2-weighted lesions with cognitive dysfunction. All MRI parameters correlated significantly with the SLICC index but not with the ECLAM index. A positive correlation was found between a cumulative dose of glucocorticoids and cerebral atrophy in SLE patients.

Conclusion: MRI abnormalities, including brain atrophy and T1- and T2-weighted lesions, are significantly more common in patients with SLE than in the general population and they are related to specific NP manifestations. Our findings also provide support for the organic aetiology of cognitive dysfunction in SLE.

Neuropsychiatric (NP) manifestations are a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE); the frequency ranging from 14% to 91% in different published series (1–4). The diagnosis of NPSLE is primarily based on the clinical picture; there is no single laboratory marker or imaging modality to serve as a golden standard (5). Despite many different types of brain magnetic resonance imaging (MRI) changes described in NPSLE, no consistent pattern of abnormality has been associated with the condition (6, 7). MRI abnormalities such as cortical stroke, global atrophy, non-specific foci of increased signal in both grey and white matter on T2-weighted images, cerebral venous thrombosis, or intracranial calcification are not specific for NPSLE (6). Furthermore, the frequent appearance of white-matter hyperintensities in normal subjects has raised questions regarding the specificity of these findings (7). The heterogeneous nature of NPSLE might be one reason for the inconsistent correlation between clinical symptoms and brain MRI findings. The study cohorts have also been heterogeneous, with some of them including patients with active and some with inactive NPSLE (6).

We have investigated a population-based sample of 43 SLE patients and an equal number of healthy controls. A clinical neurological examination and a 3-h neuropsychological investigation were undertaken for all subjects. A total of 19 of the SLE patients (44%) were diagnosed with NPSLE. Cerebral MRI, using a computer-assisted quantitative technique, was

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performed to estimate the volumes of T1- and T2-weighted lesions and cerebral atrophy.

Our primary goal was to evaluate the brain MRI findings in a population-based sample of SLE patients. The secondary goal was to detect a possible relationship between cerebral MRI abnormalities and specific NP manifestations of SLE. We also wanted to determine whether corticosteroid use is related to brain atrophy.

Methods

Patient selection

The total patient sample was the same as that described in our previous report (4). The study base was Pirkanmaa Health Care District, located in southern Finland, with a population of 440 000. We identified patients with SLE by using the computerized databases of Tampere University Hospital, the three District Hospitals, and a local outpatient clinic. Medical records of both inpatients and outpatients coded for the diagnosis of SLE between January 1980 and December 1997 were examined to select patients who fulfilled four or more of the 1982 revised American College of Rheumatology (ACR) criteria for the disease (8), were aged between 16 and 65 years, and were of native Finnish origin. Patients with another concomitant connective tissue disease were excluded.

We identified 110 patients with SLE. Of these, 15 patients had died and 37 did not meet the inclusion criteria. The remaining 58 patients were contacted by mail, and 46 of them (79%) agreed to participate in the study. The control group consisted of 46 individuals randomly identified from the Finnish Population Register, who were matched with patients for age, sex, level of education, and municipality of residence. Eligibility criteria similar to those for the patients were applied. Three patients were not able to complete the MRI investigation due to claustrophobia, and they, as well as their matched controls, were excluded from the study. All participants gave their written informed consent, and the study protocol was approved by the local ethics committee. The clinical data are shown in Table 1.

Clinical evaluation

The diagnosis of various NP syndromes was based on the clinical evaluation (HA), including review of the medical history, clinical examination, medical records, and neuropsychological testing. All past and present NP syndromes were listed and classified according to the modified ACR nomenclature and case definitions (9–10). If at least one of the NP syndromes was identified in an SLE patient, he or she was considered to have NPSLE.

All SLE patients and controls completed a 3-h battery of neuropsychological tests administered by the same psychologist; details regarding the procedure and analysis of the neuropsychological measures have been described elsewhere (4). The number of the ACR revised diagnostic criteria for SLE and current and previous use of oral glucocorticoids and other immunosuppressive medications were recorded. A cumulative lifetime dose of glucocorticoids (expressed as grams of prednisolone) was determined from the patient records. Individual disease activity was quantified using the European Consensus Lupus Activity Measurement (ECLAM) scale (11). Accumulated NP abnormalities were assessed using the Systemic Lupus International Collaborating Clinic (SLICC)/ACR damage index (12). The NP manifestations scored for the damage index included cognitive impairment, major psychosis, seizures requiring therapy for at least 6 months, cerebral vascular accident, cranial or peripheral neuropathy (excluding optic), and transverse myelitis.

Neuroradiological examinations

Cerebral MRI was performed on 43 SLE patients and 43 healthy controls. The Signa Easy Vision 1.5T

Table 1. Baseline characteristics of 43 SLE patients and 43 healthy controls (means ± SD).

	SLE patients	Controls
Age (years)	44.7 ± 12.8	44.7 ± 12.8
Sex, M/F	6/37	6/37
Education (years)	12.7 ± 2.7	12.5 ± 3.4
Number of ACR SLE criteria	5.5 ± 1.2	–
Disease duration (years)	14.5 ± 8.1	–
Number of NP syndromes	0.84 ± 1.25	0.07 ± 0.26
ECLAM score	1.58 ± 1.24	–
NP-SLICC score	0.56 ± 1.0	–
Cumulative dose of glucocorticoids (g)	15.9 ± 24.1	–

SLE, systemic lupus erythematosus; NP syndrome, neuropsychiatric syndrome; ECLAM, European Consensus Lupus Activity Measurement; NP-SLICC, Neuropsychiatric Systemic Lupus International Collaborating Clinics.

MRI imaging system (General Electric Medical Systems, Milwaukee, WS, USA) was used for all examinations. All MRI scans were read in a blinded manner by an experienced neuroradiologist (PD) who did not have access to any demographic or clinical data. The MRI study was carried out within 6 months of the clinical evaluation (the mean time was 11.1 ± 11.6 weeks for the SLE patients and 17.1 ± 7.6 weeks for the controls). The MRI protocol included sagittal T1-weighted, axial T1-weighted, axial T2-weighted, and coronal fluid-attenuated inversion recovery (FLAIR) sequences. The imaging protocol also included axial three-dimensional (3D) T2 fast spin-echo and gadolinium diethylenetriamine pentaacetic acid-enhanced 3D T1 spoiled gradient images for segmentation and volumetric analysis. Segmentation and volumetric analysis were performed using the segmentation software Anatomatic, operating in a PC/Windows95® environment (13–15). Segmentation and volumetric measurements of hypointense lesions in T1-weighted images and hyperintense lesions in T2-weighted images were performed separately.

Our criteria for SLE-related imaging abnormalities were as follows: gliotic infarcts and gliotic plaques seen as hypointense lesions on T1-weighted images and microinfarcts, ischaemic lesions, demyelinating plaques, as well as small punctate white-matter lesions localized to the periventricular and subcortical areas on T2-weighted images. Small age-related lesions were excluded from analysis. The criteria for age-related changes were as follows: small periventricular T2-weighted high-intensity signal changes in the area of the frontal and occipital horns; few scattered, well-defined, small (<3 mm), T2-weighted high-intensity signal changes in the area of the centrum semiovale not visible on T1-weighted images, and widened Virchow–Robin spaces seen as low-intensity signal areas on FLAIR images. Measurements were expressed as volume/cm^3.

The marker for cerebral atrophy was relative intracranial cerebrospinal fluid (CSF) space volume. Volumetric measurement of total CSF spaces was carried out by assessing the total volume of the ventricular and peripheral CSF spaces, expressed as volume/cm^3. Total intracranial volume was measured by adding together the volume of all the segmented grey and white matter and intracranial CSF spaces. Relative intracranial CSF space volume was determined by dividing the total intracranial CSF space volume by the total brain volume.

Inter- and intra-observer variability was studied to evaluate the accuracy of the volumetric measurement of the lesions. In the inter-observer study, sets of MRI images of 10 randomly selected patients were analysed independently by three experienced observers and one experienced neuroradiologist (PD). In the intra-observer study, the same neuroradiologist segmented the same set of MR images four times at 2-week intervals. The results were 1.0% and 3% for relative intracranial CSF space volumes, 5.0% and 1.3% for T2-weighted lesions, and 7.5% and 2.5% for T1-weighted lesions in inter-observer and intra-observer variability, respectively.

Statistical analysis

Data were analysed using the microcomputer version of the Statistical Package for Social Sciences version 11.5 (SPSS, Chicago, IL, USA). Differences in MRI parameters between the study groups were determined using the Mann–Whitney U-Test. The correlations between MRI parameters and laboratory values and cumulative dose of glucocorticoids were analysed using Spearman's rank order correlation. The criterion for statistical significance was a p-value less than 0.05.

Results

The analysis based on Anatomatic segmentation software showed that both the mean volume of T1-weighted lesions (representing primarily gliotic infarcts) and the mean volume of T2-weighted lesions were higher in SLE patients than in controls ($p=0.019$ and $p<0.0001$, respectively). In the assessment of brain atrophy it was found that the mean relative intracranial CSF space volume was significantly higher in SLE patients than in healthy controls ($p<0.001$). The values of the MRI parameters in SLE patients and controls are shown in Table 2.

Association of MRI findings with NP manifestations

The cerebral MRI parameters were determined separately in 19 patients with NPSLE and in 24 patients without (nNPSLE). All of the measured parameters were statistically significantly higher in NPSLE than in nNPSLE patients (Table 2). The relationship between MRI parameters and all but two NP manifestations was investigated in SLE patients (myasthenia gravis and polyneuropathy were excluded) (Table 3). SLE patients with cognitive impairment had more significant cerebral atrophy ($p=0.008$) and significantly larger volumes of T2-weighted lesions ($p<0.001$) and a trend for larger volumes of T1-weighted lesions ($p=0.077$) than patients who were tested as cognitively normal. The SLE patients with a history of cerebrovascular disease had increased volumes of T1-weighted lesions ($p=0.004$) and T2-weighted lesions ($p<0.001$), but also brain atrophy ($p=0.001$). SLE patients with epileptic seizures had more significant cerebral

Table 2. Cerebral MRI parameters in 43 SLE patients, 43 healthy controls, 19 patients with neuropsychiatric SLE (NPSLE) and 24 patients without neuropsychiatric SLE (nNPSLE).

MRI parameter volume (mean±SD)	SLE patients n=43	Controls n=43	p-value*	NPSLE patients n=19	nNPSLE patients n=24	p-value*
Relative intracranial CSF space volume	0.19±0.07	0.11±0.12	<0.001	0.23±0.79	0.16±0.04	0.002
T1-weighted volume, cm^3	0.47±1.42	0.09±0.30	0.019	0.73±1.76	0.27±1.01	0.007
T2-weighted volume, cm^3	1.30±0.68	0.29±0.11	<0.001	1.70±0.68	0.97±0.50	0.001

MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; CSF, cerebrospinal fluid.
*Statistical significance was based on the Mann–Whitney U-test.

Table 3. MRI volumes in the classified neuropsychiatric manifestations in 43 SLE patients.

		Relative intracranial CSF volume		T1-weighted lesions		T2-weighted lesions	
Neuropsychiatric manifestation	n	Mean	p-value*	Mean	p-value*	Mean	p-value
Cognitive dysfunction							
Yes	10	0.25	0.008	0.98	0.077	2.01	<0.001
No	33	0.17		0.32		1.08	
Cerebrovascular disease							
Yes	6	0.28	0.001	1.97	0.004	2.29	<0.001
No	37	1.18		0.23		1.13	
Seizure disorders							
Yes	4	0.33	<0.001	2.19	0.049	1.95	0.167
No	39	0.18		0.30		1.23	
Severe depression							
Yes	4	0.23	0.86	0.14	0.762	1.59	0.319
No	39	0.19		0.50		1.27	
Neuropathy, cranial							
Yes	3	0.21	0.40	0.19	0.911	1.51	0.451
No	40	0.19		0.49		1.28	
Acute confusional state							
Yes	2	0.26	0.20	3.76	0.434	2.09	0.124
No	41	0.19		0.31		1.26	
Movement disorder							
Yes	1	0.32	0.14	7.51	0.047	2.46	0.186
No	42	0.19		0.30		1.27	
Aseptic meningitis							
Yes	1	0.28	0.28	0.00	0.698	2.12	0.233
No	42	0.19		0.48		1.28	
Demyelinating syndrome							
Yes	1	0.15	0.70	0.36	0.465	1.67	0.791
No	42	0.19		0.47		1.29	

MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; CSF, cerebrospinal fluid.
*Statistical significance was based on the Mann–Whitney U-test.

atrophy than patients without ($p<0.001$) and more also T1-weighted lesions ($p=0.049$). Of the other NP manifestations, only a single patient with a movement disorder had a statistically significantly higher volume of T1-weighted lesions than the patients without ($p=0.047$). The NP damage

Table 4. Correlations of MRI volumes with various clinical features in 43 SLE patients.

MRI parameter	Age	Duration of SLE	Cumulative dose of steroid	ECLAM score	NP-SLICC score
Relative intracranial CSF space volume	0.22	0.39*	0.38*	0.040	0.69**
T1-weighted volume	0.17	0.11	0.40*	−0.23	0.52**
T2-weighted volume	0.031*	0.19	0.22	−0.024	0.69**

MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; ECLAM, European Consensus Lupus Activity Measurement; NP-SLICC, Neuropsychiatric Systemic Lupus International Collaborating Clinics. Statistical values were determined by Spearman's rank order correlation test: *$p<0.05$, **$p<0.01$.

index SLICC correlated significantly with all the measured MRI parameters in SLE patients (Table 4).

Association of MRI findings with other clinical features

Correlations between the MRI parameters and clinical features of patients (Table 4) and controls were measured. A significant correlation was detected between the duration of SLE and cerebral atrophy ($r=0.39$, $p=0.010$), but not between the disease duration and the volumes of T1- or T2-weighted lesions. The volumes of T2-weighted lesions correlated positively with age both in the SLE patients ($r=0.33$, $p=0.03$) and in the controls ($r=0.42$, $p=0.005$). A significant correlation between age and cerebral atrophy was also observed in the controls ($r=0.53$, $p=0.020$) but not in the SLE patients. No significant correlation between MRI parameters and the activity index ECLAM was found. Similarly, no association was detected between MRI parameters and the use of medication, but a clear positive correlation between the cumulative dose of glucocorticoid and parameters of cerebral atrophy was found ($p=0.023$). In SLE patients, no association was detected between the MRI parameters and laboratory findings. Instead, in the control group, a positive significant correlation was found between the volumes of T2-weighted lesions and all the measured complement levels ($r=0.31$, $p=0.04$ for C3; $r=0.49$, $p=0.001$ for C4; $r=0.36$, $p=0.02$ for CH50) and between cerebral atrophy and C4 ($r=0.44$, $p=0.003$).

Discussion

This study examined the results of volumetric MRI of the brain in 43 patients with SLE and in the same number of matched controls. Nineteen SLE patients (44%) had had NPSLE, but only one of them had an acute NP manifestation at the time of the examination.

SLE patients had more evidence of cerebral atrophy in MRI scans than the controls. Increased incidence of cerebral atrophy has previously been reported in SLE patients with and without a history of NP manifestations (7, 16–17). According to a volumetric analysis by Chinn et al (16), the mean parameter indicating atrophy was statistically significantly higher in SLE patients than in controls. The aetiology of cerebral atrophy remains unknown. It might reflect ongoing CNS involvement, resulting from long-standing glucocorticoid use, or be a combination of both of these processes (5). In our SLE patients, a clear correlation was detected between cerebral atrophy and the cumulative dose of glucocorticoids, but the current use of glucocorticoids or any other medication was unrelated to atrophic changes. Chinn et al (16) found no association between either the current or past use of steroids or the total amount of steroid used and the presence of atrophy in 47 SLE patients, but in another study, a trend for a significant relationship between cerebral atrophy and prednisone dose was observed (7).

It has been suggested that cerebral atrophy might be responsible for some of the NP manifestations related to SLE (5). We recognized that the patients with NPSLE had higher volumes, indicating cerebral atrophy, than the patients without NPSLE. Furthermore, cerebral atrophy was increased in SLE patients with cognitive dysfunction, cerebrovascular disease, and seizure disorder compared with SLE patients without these NP manifestations. Previously, no correlation has been demonstrated between quantitative measures of non-specific abnormalities in cerebral MRI and measures of brain function. Kozora et al (7) found no association between cerebral lesions measured by quantified MRI analyses and functional abnormalities determined by comprehensive neuropsychological testing in 20 SLE patients without overt central nervous system disease. However, our results are in accordance with a recent study in which the presence of cognitive dysfunction and psychiatric abnormalities in a sample of 24 patients with NPSLE correlated with cerebral atrophy (18). This study used a new sensitive MRI technique, volumetric magnetic transfer imaging (MTI). Contrary to our findings, the results did not indicate a relationship between the duration of SLE and cerebral atrophy.

In our study, the volumes of both T1- and T2-weighted lesions were significantly higher in SLE patients than in controls. Similarly, NPSLE patients had increased volumes of both lesion types in comparison with non-NPSLE patients. T1-weighted lesions include gliotic infarcts and gliotic demyelinating lesions, whereas T2-weighted lesions also include microinfarcts, ischaemic lesions, and non-gliotic demyelinating lesions. It is generally known that T2-weighted images of the brain reveal, in many SLE patients, small punctate lesions localized mainly in the periventricular and subcortical white matter. These lesions may represent small-vessel vasculopathy, which has been suggested to be a pathogenetic mechanism in those SLE patients who have cognitive disorder as a sole NP manifestation (19). Our results support this hypothesis, as volumes of T2-weighted lesions were statistically significantly higher in SLE patients with cognitive dysfunction than in those without. On the other hand, the volumes of T1-weighted lesions representing gross infarcts did not have an association with cognitive impairment.

The SLE activity index ECLAM score did not correlate with any of the MRI parameters. In two previous studies, such a correlation has been noted (20,21). These opposite findings may be due to considerably low ECLAM scores in our patients, as most of them were in good health at the time of the assessment. Instead, the NP SLICC damage index score correlated positively with all the measured MRI parameters. This is in accordance with the results of Sanna et al, who demonstrated the presence of significantly higher SLICC scores in patients with abnormal brain MRI (22). With regard to other clinical features, we found that age correlated positively with the volumes of T2-weighted lesions both in the patients and the controls.

This is one of the few studies on NPSLE with a population-based sample and a sex- and age-stratified reference group. Most of the other studies have been performed on patients from tertiary referral centres, thus causing a possible bias in the results. Our study confirms in a population-based sample that both brain atrophy and the occurrence of gliotic infarcts, microinfarcts, other ischaemic lesions, and demyelinating lesions were significantly more common in patients with SLE than in the general population. Previous studies have not been able to show any relationship between cerebral MRI abnormalities and specific NP dysfunctions. In our study, cerebral atrophy correlated with cognitive dysfunction, cerebrovascular disease, and seizure disorder. Contrary to other findings, a clear correlation was also detected between cerebral atrophy and the cumulative use of corticosteroids.

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